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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING E2A

Current *Step 4* version

dated 27 October 1994

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E2A
Document History

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E2A	Approval by the Steering Committee under *Step 2* and release for public consultation.	24 June 1993	E2A

Current *Step 4* version

E2A	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	27 October 1994	E2A

CLINICAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 27 October 1994, this guideline is recommended for adoption to the three regulatory parties to ICH

I. INTRODUCTION

It is important to harmonise the way to gather and, if necessary, to take action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in this area. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited (alert) reports and periodic safety update reporting, respectively, are important precedents and models. However, there are special circumstances involving medicinal products under development, especially in the early stages and before any marketing experience is available. Conversely, it must be recognised that a medicinal product will be under various stages of development and/or marketing in different countries, and safety data from marketing experience will ordinarily be of interest to regulators in countries where the medicinal product is still under investigational-only (Phase 1, 2, or 3) status. For this reason, it is both practical and well-advised to regard pre-marketing and post-marketing clinical safety reporting concepts and practices as interdependent, while recognising that responsibility for clinical safety within regulatory bodies and companies may reside with different departments, depending on the status of the product (investigational vs. marketed).

There are two issues within the broad subject of clinical safety data management that are appropriate for harmonisation at this time:

(1) the development of standard definitions and terminology for key aspects of clinical safety reporting, and

(2) the appropriate mechanism for handling expedited (rapid) reporting, in the investigational (i.e., pre-approval) phase.

The provisions of this guideline should be used in conjunction with other ICH Good Clinical Practice guidelines.

II. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

A. Basic Terms

Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction have previously been agreed to by consensus of the more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). [Edwards, I.R., et al, Harmonisation in Pharmacovigilance. *Drug Safety* 10(2): 93-102, 1994.] Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval, development environment.

The following definitions, with input from the WHO Collaborative Centre, have been agreed:

1. Adverse Event (or Adverse Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

2. Adverse Drug Reaction (ADR)

In the *pre-approval clinical experience* with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding *marketed medicinal products*, a well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

3. Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). (See section III.C.)

B. Serious Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

> The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

> *A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:*
>
> * *results in death,*
>
> * *is life-threatening,*
>
> *NOTE:* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
>
> * *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
>
> * *results in persistent or significant disability/incapacity, or*
>
> * *is a congenital anomaly/birth defect.*

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

C. Expectedness of an Adverse Drug Reaction

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of

previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

As stated in the definition (II.A.3.), an "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. (See section III.F. and ICH Guideline for the Investigator's Brochure.)

2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

III. STANDARDS FOR EXPEDITED REPORTING

A. What Should be Reported?

1. Single Cases of Serious, Unexpected ADRs

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) should always be specified.

Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subject to *expedited* reporting.

Information obtained by a sponsor or manufacturer on serious, unexpected reports from any source should be submitted on an expedited basis to appropriate regulatory authorities if the minimum criteria for expedited reporting can be met. See section III.B.

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

2. Other Observations

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgement should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

a. For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

b. A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.

c. A major safety finding from a newly completed animal study (such as carcinogenicity).

B. Reporting Time Frames

1. Fatal or Life-Threatening Unexpected ADRs

Certain ADRs may be sufficiently alarming so as to require very rapid notification to regulators in countries where the medicinal product or indication, formulation, or population for the medicinal product are still not approved for marketing, because such reports may lead to consideration of suspension of, or other limitations to, a clinical investigations program. Fatal or life-threatening, unexpected ADRs occurring in *clinical investigations* qualify for very rapid reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

2. All Other Serious, Unexpected ADRs

Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

3. Minimum criteria for reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: an identifiable patient; a suspect medicinal product; an identifiable reporting source; and an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Follow-up information should be actively sought and submitted as it becomes available.

C. How to Report

The CIOMS-I form has been a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain basic information/data elements, when available, be included with any expedited report, whether in a tabular or narrative presentation. The listing in Attachment 1 addresses those data elements regarded as desirable; if all are not available at the time of expedited reporting, efforts should be made to obtain them. (See section III.B.)

All reports must be sent to those regulators or other official parties requiring them (as appropriate for the local situation) in countries where the drug is under development.

D. Managing Blinded Therapy Cases

When the sponsor and investigator are blinded to individual patient treatment (as in a double-blind study), the occurrence of a serious event requires a decision on whether to open (break) the code for the specific patient. If the investigator breaks the blind, then it is assumed the sponsor will also know the assigned treatment for that patient. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.

There are several disadvantages to maintaining the blind under the circumstances described which outweigh the advantages. By retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory data bases are revised. If the event is serious, new, and possibly related to the medicinal product, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading. Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data.

However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it

may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

E. Miscellaneous Issues

1. Reactions Associated with Active Comparator or Placebo Treatment

It is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies. Sponsors must report such events to either the manufacturer of the active control or to appropriate regulatory agencies. Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.

2. Products with More than one Presentation or Use

To avoid ambiguities and uncertainties, an ADR that qualifies for expedited reporting with one presentation of a product (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or referenced to regulatory filings across other product presentations and uses.

It is not uncommon that more than one dosage form, formulation, or delivery system (oral, IM, IV, topical, etc.) of the pharmacologically active compound(s) is under study or marketed; for these different presentations there may be some marked differences in the clinical safety profile. The same may apply for a given product used in different indications or populations (single dose vs. chronic administration, for example). Thus, "expectedness" may be product or product-use specific, and separate Investigator's Brochures may be used accordingly. However, such documents are expected to cover ADR information that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product-specific or use-specific safety information will also be included.

It is recommended that any adverse drug reactions that qualify for expedited reporting observed with one product dosage form or use be cross referenced to regulatory records for all other dosage forms and uses for that product. This may result in a certain amount of overreporting or unnecessary reporting in obvious situations (for example, a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed). However, underreporting is completely avoided.

3. Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

F. INFORMING INVESTIGATORS AND ETHICS COMMITTEES/ INSTITUTIONAL REVIEW BOARDS OF NEW SAFETY INFORMATION

International standards regarding such communication are discussed within the ICH GCP Guidelines, including the addendum on "Guideline for the Investigator's Brochure." In general, the sponsor of a study should amend the Investigator's Brochure as needed, and in accord with any local regulatory requirements, so as to keep the description of safety information updated.

Attachment 1

KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details

Initials

Other relevant identifier (clinical investigation number, for example)

Gender

Age and/or date of birth

Weight

Height

2. Suspected Medicinal Product(s)

Brand name as reported

International Non-Proprietary Name (INN)

Batch number

Indication(s) for which suspect medicinal product was prescribed or tested

Dosage form and strength

Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)

Route of administration

Starting date and time of day

Stopping date and time, or duration of treatment

3. Other Treatment(s)

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.

Start date (and time) of onset of reaction

Stop date (and time) or duration of reaction

Dechallenge and rechallenge information

Setting (e.g., hospital, out-patient clinic, home, nursing home)

Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. Details on Reporter of Event (Suspected ADR)

Name

Address

Telephone number

Profession (speciality)

6. Administrative and Sponsor/Company Details

Source of report: was it spontaneous, from a clinical investigation (provide details), from the literature (provide copy), other?

Date event report was first received by sponsor/manufacturer

Country in which event occurred

Type of report filed to authorities: initial or follow-up (first, second, etc.)

Name and address of sponsor/manufacturer/company

Name, address, telephone number, and FAX number of contact person in reporting company or institution

Identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND or CTX number, NDA number)

Sponsor/manufacturer's identification number for the case (this number must be the same for the initial and follow-up reports on the same case).

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)

Current *Step 4* version

dated 10 June 1996

(including the Post Step 4 corrections)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E6(R1)
Document History

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E6	Approval by the Steering Committee under *Step 4* and recommended for adoption to the three ICH regulatory bodies.	1 May 1996	E6

Current *Step 4* version

E6	Approval by the Steering Committee of *Post-Step 4* editorial corrections.	10 June 1996	E6(R1)

GUIDELINE FOR GOOD CLINICAL PRACTICE

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 1 May 1996, this guideline is recommended for adoption to the three regulatory parties to ICH

(This document includes the Post Step 4 corrections agreed by the Steering Committee on 10 June 1996)

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GUIDELINE FOR GOOD CLINICAL PRACTICE

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable

opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

1.37 Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record

See Source Documents.

1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,

- is life-threatening,

- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site

The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;

- modifications required prior to its approval/favourable opinion;

- disapproval / negative opinion; and

- termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or

administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the

IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally

acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the

applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

(b) Maintains SOPs for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see 4.1.4) and

(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the

safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

  (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

  (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

  (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

  (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

  (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enroling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents

An example of the Table of Contents is given in Appendix 2

7.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug

reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 APPENDIX 1:

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 APPENDIX 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter

Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT**		X	X
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.5	**INSURANCE STATEMENT** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.:	To document agreements		
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO		X	X
	- sponsor and CRO			(where required) X
	- investigator/institution and authority(ies) (where required)		X	X
8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.8	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X
8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**
	- protocol amendment(s)
	- revision(s) of:
	  - informed consent form
	  - any other written information to be provided to the subject
	  - advertisement for subject recruitment (if used)
	- any other documents given approval/favourable opinion
	- continuing review of trial (where required)
		To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X
8.3.6	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 8.2.15.)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.20	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.4.7	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	X (if applicable)	X

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL TRIALS
E8

Current *Step 4* version

dated 17 July 1997

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E8
Document History

First Codification	History	Date	New Codification **November 2005**
E8	Approval by the Steering Committee under *Step 2* and release for public consultation.	7 November 1996	E8

Current *Step 4* version

E8	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	17 July 1997	E8

GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 17 July 1997, this guideline is recommended for adoption to the three regulatory parties to ICH

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GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

1. OBJECTIVES OF THIS DOCUMENT

In the three ICH regions, the evolution of drug development strategies and evaluation processes has led to the establishment of regional guidances on general considerations for clinical trials and the process of clinical development of pharmaceuticals for human use. This harmonised guideline is derived from those regional documents as well as from ICH Guidelines.

The ICH document "General Considerations for Clinical Trials" is intended to:

(a) describe internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategy for new medicinal products.

(b) facilitate the evaluation and acceptance of foreign clinical trial data by promoting common understanding of general principles, general approaches and the definition of relevant terms.

c) present an overview of the ICH clinical safety and efficacy documents and facilitate the user's access to guidance pertinent to clinical trials within these documents. The relevant ICH documents are listed in Annex 1.

(d) provide a separate glossary of terms used in the ICH clinical safety and efficacy related documents that pertain to clinical trials and indicate which documents contain them.

For the sake of brevity, the term "drug" has been used in this document. It should be considered synonymous with "investigational (medicinal) product", "medicinal product" and "pharmaceutical" including vaccines and other biological products. The principles established in this guideline may also be applied to other clinical investigations (e.g. radiotherapy, psychotherapy, surgery, medical devices and alternative therapies).

2. GENERAL PRINCIPLES

2.1 Protection of clinical trial subjects

The principles and practices concerning protection of trial subjects are stated in the ICH Guideline on Good Clinical Practice (ICH E6). These principles have their origins in The Declaration of Helsinki and should be observed in the conduct of all human drug investigations.

Before any clinical trial is carried out, results of non-clinical investigations or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans. The purpose and timing of animal pharmacology and toxicology studies intended to support studies of a given duration are discussed in ICH M3. The role of such studies for biotechnology products is cited in ICH S6.

Throughout drug development, emerging animal toxicological and clinical data should be reviewed and evaluated by qualified experts to assess their implications for the safety of the trial subjects. In response to such findings, future studies and, when necessary, those in progress should be appropriately modified in a timely fashion to maintain the safety of trial participants. The investigator and sponsor share responsibility for the protection of clinical trial subjects together with the

Institutional Review Board/Independent Ethics Committee. The responsibilities of these parties are described in ICH E6.

2.2 Scientific approach in design and analysis

Clinical trials should be designed, conducted and analysed according to sound scientific principles to achieve their objectives; and should be reported appropriately. The essence of rational drug development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified according to when the study occurs during clinical development or as shown in Table 1 by their objectives. (The illustrative examples are not intended to be exhaustive). The cardinal logic behind serially conducted studies of a medicinal product is that the results of prior studies should influence the plan of later studies. Emerging data will frequently prompt a modification of the development strategy. For example, results of a therapeutic confirmatory study may suggest a need for additional human pharmacology studies.

The availability of foreign clinical data should obviate the need to generate similar data in an ICH region if the ICH E5 and ICH E6 guidelines are followed. (see ICH E5).

Table 1 - An Approach to Classifying Clinical Studies According to Objective

Type of Study	*Objective of Study*	*Study Examples*
Human Pharmacology	• Assess tolerance • Define/describe PK[1] and PD[2] • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies
Therapeutic Exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest trials of relatively short duration in well- defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose-response exploration studies
Therapeutic Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Adequate, and well controlled studies to establish efficacy • Randomised parallel dose-response studies • Clinical safety studies • Studies of mortality/ morbidity outcomes • Large simple trials • Comparative studies
Therapeutic Use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

[1]Pharmacokinetics
[2]Pharmacodynamics

3. DEVELOPMENT METHODOLOGY

This section covers issues and considerations relating to the development plan and to its individual component studies.

3.1 Considerations for the Development Plan

3.1.1 Non-Clinical Studies

Important considerations for determining the nature of non-clinical studies and their timing with respect to clinical trials include:

a) duration and total exposure proposed in individual patients

b) characteristics of the drug (e.g. long half life, biotechnology products)

c) disease or condition targeted for treatment

d) use in special populations (e.g. women of childbearing potential)

e) route of administration

The need for non-clinical information including toxicology, pharmacology and pharmacokinetics to support clinical trials is addressed in the ICH M3 and S6 documents.

3.1.1.1 Safety Studies

For the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite non-clinical pharmacokinetic, pharmacological and toxicological evaluations (see ICH M3). Early non-clinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about physiological and toxicological effects of a new drug.

3.1.1.2 Pharmacological and Pharmacokinetic Studies

The basis and direction of the clinical exploration and development rests on the non-clinical pharmacokinetic and pharmacology profile, which includes information such as:

a) Pharmacological basis of principal effects (mechanism of action).

b) Dose-response or concentration-response relationships and duration of action

c) Study of the potential clinical routes of administration

d) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses

e) Studies of absorption, distribution, metabolism and excretion

3.1.2 Quality of Investigational Medicinal Products

Formulations used in clinical trials should be well characterised, including information on bioavailability wherever feasible. The formulation should be appropriate for the stage of drug development. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses. During drug development different formulations of a drug may be tested. Links between formulations, established by bioequivalence studies or other means are important in interpreting clinical study results across the development program.

3.1.3 Phases of Clinical Development

Clinical drug development is often described as consisting of four temporal phases (Phase I-IV). It is important to recognise that the phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases (see Fig 1.). A classification system using study objectives as discussed in section 2.2 is preferable. It is important to appreciate that the phase concept is a description, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies since for some drugs in a development plan the typical sequence will not be appropriate or necessary. For example, although human pharmacology studies are typically conducted during Phase I, many such studies are conducted at each of the other three stages, but nonetheless sometimes labelled as Phase I studies. Figure 1 demonstrates this close but variable correlation between the two classification systems. The distribution of the points of the graph shows that the types of study are not synonymous with the phases of development.

Correlation between Development Phases and Types of Study

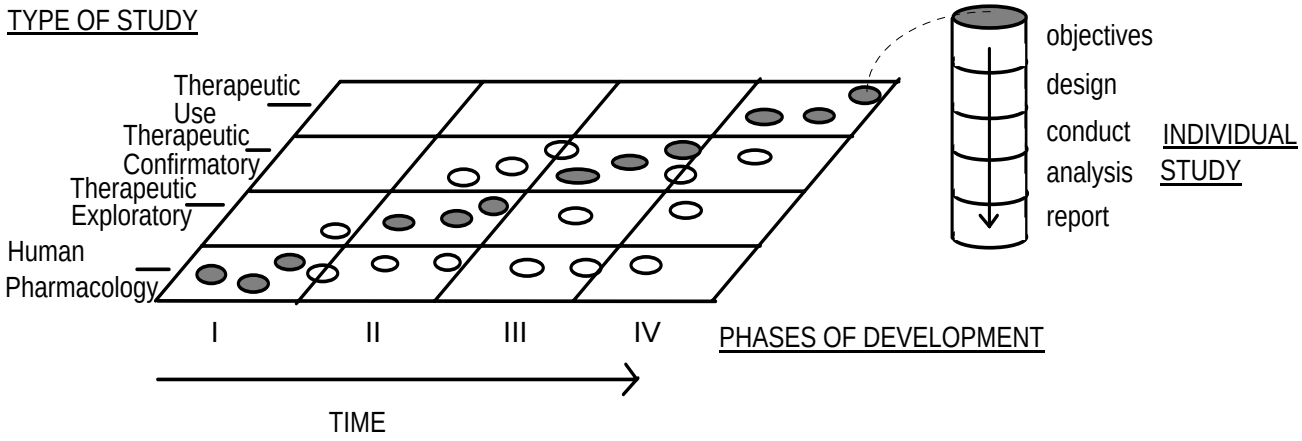

Figure 1 *- This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study.*

Drug development is ideally a logical, step-wise procedure in which information from small early studies is used to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify characteristics of the investigational medicine in the early stages of development and to plan an appropriate development based on this profile.

Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials. Later confirmatory studies are generally larger and longer and include a more

diverse patient population. Dose-response information should be obtained at all stages of development, from early tolerance studies, to studies of short-term pharmacodynamic effect, to large efficacy studies (see ICH E4). Throughout development, new data may suggest the need for additional studies that are typically part of an earlier phase. For example, blood level data in a late trial may suggest a need for a drug-drug interaction study, or adverse effects may suggest the need for further dose finding and/or additional non-clinical studies. In addition, to support a new marketing application approval for the same drug e.g. for a new indication, pharmacokinetic or therapeutic exploratory studies are considered to be in Phase I or Phase II of development.

3.1.3.1 Phase I (Most typical kind of study: Human Pharmacology)

Phase I starts with the initial administration of an investigational new drug into humans.

Although human pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients, e.g. patients with mild hypertension. Drugs with significant potential toxicity, e.g. cytotoxic drugs, are usually studied in patients. Studies in this phase can be open, baseline controlled or may use randomisation and blinding, to improve the validity of observations.

Studies conducted in Phase I typically involve one or a combination of the following aspects:

a) Estimation of Initial Safety and Tolerability

The initial and subsequent administration of an investigational new drug into humans is usually intended to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies typically include both single and multiple dose administration.

b) Pharmacokinetics

Characterisation of a drug's absorption, distribution, metabolism, and excretion continues throughout the development plan**.** Their preliminary characterisation is an important goal of Phase I. Pharmacokinetics may be assessed via separate studies or as a part of efficacy, safety and tolerance studies. Pharmacokinetic studies are particularly important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites and potential drug-drug interactions. Some pharmacokinetic studies are commonly conducted in later phases to answer more specialised questions. For many orally administered drugs, especially modified release products, the study of food effects on bioavailability is important. Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, women and ethnic subgroups should be considered. Drug-drug interaction studies are important for many drugs; these are generally performed in phases beyond Phase I but studies in animals and in vitro studies of metabolism and potential interactions may lead to doing such studies earlier.

c) Assessment of Pharmacodynamics

Depending on the drug and the endpoint studied, pharmacodynamic studies and studies relating drug blood levels to response (PK/PD studies) may be conducted in

healthy volunteer subjects or in patients with the target disease. In patients, if there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies.

d) Early Measurement of Drug Activity

Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

3.1.3.2 Phase II (Most typical kind of study: Therapeutic Exploratory)

Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients.

Initial therapeutic exploratory studies may use a variety of study designs, including concurrent controls and comparisons with baseline status. Subsequent trials are usually randomised and concurrently controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication. Studies in Phase II are typically conducted in a group of patients who are selected by relatively narrow criteria**,** leading to a relatively homogeneous population and are closely monitored.

An important goal for this phase is to determine the dose(s) and regimen for Phase III trials. Early studies in this phase often utilise dose escalation designs (see ICH E4) to give an early estimate of dose response and later studies may confirm the dose response relationship for the indication in question by using recognised parallel dose-response designs (could also be deferred to phase III). Confirmatory dose response studies may be conducted in Phase II or left for Phase III. Doses used in Phase II are usually but not always less than the highest doses used in Phase I.

Additional objectives of clinical trials conducted in Phase II may include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further study in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

3.1.3.3 Phase III (Most typical kind of study: Therapeutic Confirmatory)

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit.

Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies are intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug. For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be started in Phase II (see ICH E1). ICH E1 and ICH E7 describe the overall clinical safety database considerations for chronically administered drugs and drugs used in the elderly. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (official product information).

3.1.3.4 Phase IV (Variety of Studies: - Therapeutic Use)

Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy and dose definition.

Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies.

3.1.3.5 Development of an application unrelated to original approved use

After initial approval, drug development may continue with studies of new or modified indications, new dosage regimens, new routes of administration or additional patient populations. If a new dose, formulation or combination is studied, additional human pharmacology studies may be indicated, necessitating a new development plan.

The need for some studies may be obviated by the availability of data from the original development plan or from therapeutic use.

3.1.4 Special Considerations

A number of special circumstances and populations require consideration on their own when they are part of the development plan.

3.1.4.1 Studies of Drug Metabolites

Major active metabolite(s) should be identified and deserve detailed pharmacokinetic study. Timing of the metabolic assessment studies within the development plan depends on the characteristics of the individual drug.

3.1.4.2 Drug-Drug Interactions

If a potential for drug-drug interaction is suggested by metabolic profile, by the results of non-clinical studies or by information on similar drugs, studies on drug interaction during clinical development are highly recommended. For drugs that are frequently co-administered it is usually important that drug-drug interaction studies be performed in non-clinical and, if appropriate in human studies. This is particularly true for drugs that are known to alter the absorption or metabolism of other drugs (see ICH E7), or whose metabolism or excretion can be altered by effects by other drugs.

3.1.4.3 Special Populations

Some groups in the general population may require special study because they have unique risk/benefit considerations that need to be taken into account during drug development, or because they can be anticipated to need modification of use of the dose or schedule of a drug compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of potentially altered drug metabolism or excretion. Other ICH documents address such issues for geriatric patients (ICH E7) and patients from different ethnic groups (ICH E5). The need for non-clinical safety studies to support human clinical trials in special populations is addressed in the ICH M3 document.

Particular attention should be paid to the ethical considerations related to informed consent from vulnerable populations and the procedures scrupulously followed.(see ICH E6)

a) Investigations in pregnant women

In general, pregnant women should be excluded from clinical trials where the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up evaluation of the pregnancy, foetus, and child is very important . Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus, and child is very important.

b) Investigations in nursing women

Excretion of the drug or its metabolites into human milk should be examined where applicable. When nursing mothers are enrolled in clinical studies their babies should be monitored for the effects of the drug.

c) Investigations in children.

The extent of the studies needed depends on the current knowledge of the drug and the possibility of extrapolation from adults and children of other age groups. Some drugs may be used in children from the early stages of drug development (see ICH M3).

For a drug expected to be used in children, evaluation should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

3.2 Considerations for Individual Clinical Trials

The following important principles should be followed in planning the objectives, design, conduct, analysis and reporting of a clinical trial (see ICH guidelines in Annex 1). Each part should be defined in a written protocol before the study starts (see ICH E6).

3.2.1 Objectives

The objective(s) of the study should be clearly stated and may include exploratory or confirmatory characterisation of safety and/or efficacy and/or assessment of pharmacokinetic parameters and pharmacological, physiological, biochemical effects.

3.2.2 Design

The appropriate study design should be chosen to provide the desired information. Examples of study design include parallel group, cross-over, factorial, dose escalation, and fixed dose-dose response. (See ICH E4, E6, E9 and E10). Appropriate comparators should be utilised and adequate numbers of subjects included to achieve the study objectives. Primary and secondary endpoints and plans for their analyses should be clearly stated (see ICH E9). The methods of monitoring adverse events by changes in clinical signs and symptoms and laboratory studies should be described (see ICH E3). The protocol should specify procedures for the follow-up of patients who stop treatment prematurely.

3.2.2.1 Selection of subjects

The stage of development and the indication to be studied and should be taken into account in selecting the subject population (e.g. normal healthy subjects, cancer patients or other special populations in early phase development) as should prior non-clinical and clinical knowledge. The variability of groups of patients or healthy volunteers studied in early trials may be limited to a narrow range by strict selection criteria, but as drug development proceeds, the populations tested should be broadened to reflect the target population.

Depending on the stage of development and level of concern for safety, it may be necessary to conduct studies in a closely monitored (i.e., inpatient) environment.

As a general principle trial subjects should not participate concurrently in more than one clinical trial but there can be justified exceptions. Subjects should not be enrolled repetitively in clinical trials without time off treatment adequate to protect safety and exclude carry-over effects.

In general, women of childbearing potential should be using highly effective contraception to participate in clinical trials (see ICH M3).

For male subjects, potential hazards of drug exposure in the trial to their sexual partners or resulting progeny should be considered. When indicated (e.g. trials involving drugs which are potentially mutagenic, or toxic to the reproductive system), an appropriate contraception provision should be included in the trial.

3.2.2.2 Selection of Control Group

Trials should have an adequate control group. Comparisons may be made with placebo, no treatment, active controls or of different doses of the drug under investigation. The choice of the comparator depends, among other things, on the objective of the trial (see ICH E9 and E10). Historical (external) controls can be justified in some cases but particular care is important to minimise the likelihood of erroneous inference.

3.2.2.3 Number of subjects

The size of a trial is influenced by the disease to be investigated, the objective of the study and the study endpoints. Statistical assessments of sample size should be based on the expected magnitude of the treatment effect, the variability of the data, the specified (small) probability of error (see ICH E9) and the desire for information or subsets of the population or secondary endpoints.. In some circumstances a larger database may be needed to establish the safety of a drug. ICH E1 and ICH E7 suggest a minimum experience to assess safety for a registrational database for a new indication. These numbers should not be considered as absolute and may be insufficient in some cases (e.g. where long-term use in healthy individuals is expected).

3.2.2.4 Response Variables

Response variables should be defined prospectively, giving descriptions of methods of observation and quantification. Objective methods of observation should be used where possible and when appropriate (see ICH E9).

Study endpoints are the response variables that are chosen to assess drug effects that are related to pharmacokinetic parameters, pharmacodynamic measures, efficacy and safety. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess

other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analysis should be prospectively specified in the protocol.

A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

3.2.2.5 Methods to Minimise or Assess Bias

The protocol should specify methods of allocation to treatment groups and blinding (see ICH E9 and E10).

a) Randomisation

In conducting a controlled trial**,** randomised allocation is the preferred means of assuring comparability of test groups and minimising the possibility of selection bias.

b) Blinding

Blinding is an important means of reducing or minimising the risk of biased study outcomes. A trial where the treatment assignment is not known by the study participant because of the use of placebo or other methods of masking the intervention, is referred to as a single blind study. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and analysis of data are also unaware of the treatment assignments, the study is double blind.

c) Compliance

Methods used to evaluate patient usage of the test drug should be specified in the protocol and the actual usage documented.

3.2.3 Conduct

The study should be conducted according to the principles described in this guideline and in accordance with other pertinent elements outlined in ICH E6 and other relevant ICH guidelines (see Annex 1). Adherence to the study protocol is essential. If modification of the protocol becomes necessary a clear description of the rationale for the modification should be provided in a protocol amendment (see ICH E6). Timely adverse event reporting during a study is essential and should be documented. Guidance is available on expedited reporting of safety data to appropriate officials and on the content of safety reports and on privacy and confidentiality of data (see ICH E2A and E2B and ICH E6).

3.2.4 Analysis

The study protocol should have a specified analysis plan that is appropriate for the objectives and design of the study, taking into account the method of subject allocation, the measurement methods of response variables, specific hypotheses to be tested, and analytical approaches to common problems including early study withdrawal and protocol violations. A description of the statistical methods to be employed, including timing of any planned interim analysis(es) should be included in the protocol (see ICH E3**,** ICH E6 and ICH E9).

The results of a clinical trial should be analysed in accordance with the plan prospectively stated in the protocol and all deviations from the plan should be indicated in the study report. Detailed guidance is available in other ICH guidelines on planning of the protocol (ICH E6), on the analysis plan and statistical analysis of results (ICH E9) and on study reports (ICH E3).

Studies are normally expected to run to completion, although in some studies the possibility of early stopping is formally recognised. In such cases this should be clearly described in the protocol with due statistical attention to the overall levels of statistical significance and to the need to adjust the estimates of the size of treatment effects (ICH E9).

Safety data should be collected for all clinical trials, appropriately tabulated and with adverse events classified according to their seriousness and their likely causal relationship (see ICH E2A).

3.2.5 Reporting

Clinical study reports should be adequately documented following the approaches outlined in other ICH guidelines (see E3 and E6).

ANNEX

LIST OF RELEVANT ICH GUIDELINES AND TOPICS

Code	***Topic***
E1	The Extent of Population Exposure to Assess Clinical Safety for Drug Intended for Long-term Treatment of Non-Life-Threatening Conditions
E2A	Clinical Safety Data Management: Definitions and Standards for expedited Reporting
E2B	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E3	Structure and Content of Clinical Study Reports
E4	Dose-Response Information to Support Drug Registration
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6	Good Clinical Practice: Consolidated Guideline
E7	Studies in Support of Special Populations: Geriatrics
E8	General Considerations for Clinical Trials
E9	Statistical Considerations in the Design of Clinical Trials
E10	Choice of Control Group in Clinical Trials
M3	Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
S6	Safety Studies for Biotechnology-Derived Products

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version

dated 5 February 1998

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E9
Document History

First Codification	History	Date	New Codification **November 2005**
E9	Approval by the Steering Committee under *Step 2* and release for public consultation.	16 January 1997	E9

Current *Step 4* version

E9	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	5 February 1998	E9

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 5 February 1998, this guideline is recommended for adoption to the three regulatory parties to ICH

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STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

I. INTRODUCTION

1.1 Background and Purpose

The efficacy and safety of medicinal products should be demonstrated by clinical trials which follow the guidance in 'Good Clinical Practice: Consolidated Guideline' (ICH E6) adopted by the ICH, 1 May 1996. The role of statistics in clinical trial design and analysis is acknowledged as essential in that ICH guideline. The proliferation of statistical research in the area of clinical trials coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on statistical issues related to clinical trials. This guidance is written primarily to attempt to harmonise the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

As a starting point, this guideline utilised the CPMP (Committee for Proprietary Medicinal Products) Note for Guidance entitled 'Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products' (December, 1994). It was also influenced by 'Guidelines on the Statistical Analysis of Clinical Studies' (March, 1992) from the Japanese Ministry of Health and Welfare and the U.S. Food and Drug Administration document entitled 'Guideline for the Format and Content of the Clinical and Statistical Sections of a New Drug Application' (July, 1988). Some topics related to statistical principles and methodology are also embedded within other ICH guidelines, particularly those listed below. The specific guidance that contains related text will be identified in various sections of this document.

E1A:	The Extent of Population Exposure to Assess Clinical Safety
E2A:	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B:	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C:	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E3:	Structure and Content of Clinical Study Reports
E4:	Dose-Response Information to Support Drug Registration
E5:	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6:	Good Clinical Practice: Consolidated Guideline
E7:	Studies in Support of Special Populations: Geriatrics
E8:	General Considerations for Clinical Trials
E10:	Choice of Control Group in Clinical Trials
M1:	Standardisation of Medical Terminology for Regulatory Purposes
M3:	Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

This guidance is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development. The document will also assist scientific experts charged with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development.

1.2 Scope and Direction

The focus of this guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor. Integration of data across clinical trials is discussed, but is not a primary focus of this guidance. Selected principles and procedures related to data management or clinical trial monitoring activities are covered in other ICH guidelines and are not addressed here.

This guidance should be of interest to individuals from a broad range of scientific disciplines. However, it is assumed that the actual responsibility for all statistical work associated with clinical trials will lie with an appropriately qualified and experienced statistician, as indicated in ICH E6. The role and responsibility of the trial statistician (see Glossary), in collaboration with other clinical trial professionals, is to ensure that statistical principles are applied appropriately in clinical trials supporting drug development. Thus, the trial statistician should have a combination of education/training and experience sufficient to implement the principles articulated in this guidance.

For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial. The protocol and subsequent amendments should be approved by the responsible personnel, including the trial statistician. The trial statistician should ensure that the protocol and any amendments cover all relevant statistical issues clearly and accurately, using technical terminology as appropriate.

The principles outlined in this guidance are primarily relevant to clinical trials conducted in the later phases of development, many of which are confirmatory trials of efficacy. In addition to efficacy, confirmatory trials may have as their primary variable a safety variable (e.g. an adverse event, a clinical laboratory variable or an electrocardiographic measure), a pharmacodynamic or a pharmacokinetic variable (as in a confirmatory bioequivalence trial). Furthermore, some confirmatory findings may be derived from data integrated across trials, and selected principles in this guidance are applicable in this situation. Finally, although the early phases of drug development consist mainly of clinical trials that are exploratory in nature, statistical principles are also relevant to these clinical trials. Hence, the substance of this document should be applied as far as possible to all phases of clinical development.

Many of the principles delineated in this guidance deal with minimising bias (see Glossary) and maximising precision. As used in this guidance, the term 'bias' describes the systematic tendency of any factors associated with the design, conduct, analysis and interpretation of the results of clinical trials to make the estimate of a treatment effect (see Glossary) deviate from its true value. It is important to identify potential sources of bias as completely as possible so that attempts to limit such bias may be made. The presence of bias may seriously compromise the ability to draw valid conclusions from clinical trials.

Some sources of bias arise from the design of the trial, for example an assignment of treatments such that subjects at lower risk are systematically assigned to one treatment. Other sources of bias arise during the conduct and analysis of a clinical trial. For example, protocol violations and exclusion of subjects from analysis based upon knowledge of subject outcomes are possible sources of bias that may affect the accurate assessment of the treatment effect. Because bias can occur in subtle or unknown ways and its effect is not measurable directly, it is important to evaluate the robustness of the results and primary conclusions of the trial. Robustness is a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches. The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or inference.

Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate: the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust.

II. CONSIDERATIONS FOR OVERALL CLINICAL DEVELOPMENT

2.1 Trial Context

2.1.1 Development Plan

The broad aim of the process of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be simultaneously safe and effective, to the extent that the risk-benefit relationship is acceptable. The particular subjects who may benefit from the drug, and the specific indications for its use, also need to be defined.

Satisfying these broad aims usually requires an ordered programme of clinical trials, each with its own specific objectives (see ICH E8). This should be specified in a clinical plan, or a series of plans, with appropriate decision points and flexibility to allow modification as knowledge accumulates. A marketing application should clearly describe the main content of such plans, and the contribution made by each trial. Interpretation and assessment of the evidence from the total programme of trials involves synthesis of the evidence from the individual trials (see Section 7.2). This is facilitated by ensuring that common standards are adopted for a number of features of the trials such as dictionaries of medical terms, definition and timing of the main measurements, handling of protocol deviations and so on. A statistical summary, overview or meta-analysis (see Glossary) may be informative when medical questions are addressed in more than one trial. Where possible this should be envisaged in the plan so that the relevant trials are clearly identified and any necessary common features of their designs are specified in advance. Other major statistical issues (if any) that are expected to affect a number of trials in a common plan should be addressed in that plan.

2.1.2 Confirmatory Trial

A confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety. In such trials the key hypothesis of interest follows directly from the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete. In a confirmatory trial it is equally important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance.

Confirmatory trials are intended to provide firm evidence in support of claims and hence adherence to protocols and standard operating procedures is particularly important; unavoidable changes should be explained and documented, and their effect examined. A justification of the design of each such trial, and of other important statistical aspects such as the principal features of the planned analysis, should be set out in the protocol. Each trial should address only a limited number of questions.

Firm evidence in support of claims requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. The confirmatory trials should therefore be sufficient to answer each key clinical question relevant to the efficacy or safety claim clearly and definitively. In addition, it is important that the basis for generalisation (see Glossary) to the intended patient population is understood and explained; this may also influence the number and type (e.g. specialist or general practitioner) of centres and/or trials needed. The results of the confirmatory trial(s) should be robust. In some circumstances the weight of evidence from a single confirmatory trial may be sufficient.

2.1.3 Exploratory Trial

The rationale and design of confirmatory trials nearly always rests on earlier clinical work carried out in a series of exploratory studies. Like all clinical trials, these exploratory studies should have clear and precise objectives. However, in contrast to confirmatory trials, their objectives may not always lead to simple tests of pre-defined hypotheses. In addition, exploratory trials may sometimes require a more flexible approach to design so that changes can be made in response to accumulating results. Their analysis may entail data exploration; tests of hypothesis may be carried out, but the choice of hypothesis may be data dependent. Such trials cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence.

Any individual trial may have both confirmatory and exploratory aspects. For example, in most confirmatory trials the data are also subjected to exploratory analyses which serve as a basis for explaining or supporting their findings and for suggesting further hypotheses for later research. The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis.

2.2 Scope of Trials

2.2.1 Population

In the earlier phases of drug development the choice of subjects for a clinical trial may be heavily influenced by the wish to maximise the chance of observing specific clinical effects of interest, and hence they may come from a very narrow subgroup of the total patient population for which the drug may eventually be indicated. However by the time the confirmatory trials are undertaken, the subjects in the trials should

more closely mirror the target population. Hence, in these trials it is generally helpful to relax the inclusion and exclusion criteria as much as possible within the target population, while maintaining sufficient homogeneity to permit precise estimation of treatment effects. No individual clinical trial can be expected to be totally representative of future users, because of the possible influences of geographical location, the time when it is conducted, the medical practices of the particular investigator(s) and clinics, and so on. However the influence of such factors should be reduced wherever possible, and subsequently discussed during the interpretation of the trial results.

2.2.2 Primary and Secondary Variables

The primary variable ('target' variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. There should generally be only one primary variable. This will usually be an efficacy variable, because the primary objective of most confirmatory trials is to provide strong scientific evidence regarding efficacy. Safety/tolerability may sometimes be the primary variable, and will always be an important consideration. Measurements relating to quality of life and health economics are further potential primary variables. The selection of the primary variable should reflect the accepted norms and standards in the relevant field of research. The use of a reliable and validated variable with which experience has been gained either in earlier studies or in published literature is recommended. There should be sufficient evidence that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria. The primary variable should generally be the one used when estimating the sample size (see section 3.5).

In many cases, the approach to assessing subject outcome may not be straightforward and should be carefully defined. For example, it is inadequate to specify mortality as a primary variable without further clarification; mortality may be assessed by comparing proportions alive at fixed points in time, or by comparing overall distributions of survival times over a specified interval. Another common example is a recurring event; the measure of treatment effect may again be a simple dichotomous variable (any occurrence during a specified interval), time to first occurrence, rate of occurrence (events per time units of observation), etc. The assessment of functional status over time in studying treatment for chronic disease presents other challenges in selection of the primary variable. There are many possible approaches, such as comparisons of the assessments done at the beginning and end of the interval of observation, comparisons of slopes calculated from all assessments throughout the interval, comparisons of the proportions of subjects exceeding or declining beyond a specified threshold, or comparisons based on methods for repeated measures data. To avoid multiplicity concerns arising from post hoc definitions, it is critical to specify in the protocol the precise definition of the primary variable as it will be used in the statistical analysis. In addition, the clinical relevance of the specific primary variable selected and the validity of the associated measurement procedures will generally need to be addressed and justified in the protocol.

The primary variable should be specified in the protocol, along with the rationale for its selection. Redefinition of the primary variable after unblinding will almost always be unacceptable, since the biases this introduces are difficult to assess. When the clinical effect defined by the primary objective is to be measured in more than one way, the protocol should identify one of the measurements as the primary variable on

the basis of clinical relevance, importance, objectivity, and/or other relevant characteristics, whenever such selection is feasible.

Secondary variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives. Their pre-definition in the protocol is also important, as well as an explanation of their relative importance and roles in interpretation of trial results. The number of secondary variables should be limited and should be related to the limited number of questions to be answered in the trial.

2.2.3 Composite Variables

If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or 'composite' variable, using a pre-defined algorithm. Indeed, the primary variable sometimes arises as a combination of multiple clinical measurements (e.g. the rating scales used in arthritis, psychiatric disorders and elsewhere). This approach addresses the multiplicity problem without requiring adjustment to the type I error. The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit. When a composite variable is used as a primary variable, the components of this variable may sometimes be analysed separately, where clinically meaningful and validated. When a rating scale is used as a primary variable, it is especially important to address such factors as content validity (see Glossary), inter- and intra-rater reliability (see Glossary) and responsiveness for detecting changes in the severity of disease.

2.2.4 Global Assessment Variables

In some cases, 'global assessment' variables (see Glossary) are developed to measure the overall safety, overall efficacy, and/or overall usefulness of a treatment. This type of variable integrates objective variables and the investigator's overall impression about the state or change in the state of the subject, and is usually a scale of ordered categorical ratings. Global assessments of overall efficacy are well established in some therapeutic areas, such as neurology and psychiatry.

Global assessment variables generally have a subjective component. When a global assessment variable is used as a primary or secondary variable, fuller details of the scale should be included in the protocol with respect to:

1) the relevance of the scale to the primary objective of the trial;

2) the basis for the validity and reliability of the scale;

3) how to utilise the data collected on an individual subject to assign him/her to a unique category of the scale;

4) how to assign subjects with missing data to a unique category of the scale, or otherwise evaluate them.

If objective variables are considered by the investigator when making a global assessment, then those objective variables should be considered as additional primary, or at least important secondary, variables.

Global assessment of usefulness integrates components of both benefit and risk and reflects the decision making process of the treating physician, who must weigh benefit and risk in making product use decisions. A problem with global usefulness variables is that their use could in some cases lead to the result of two products being

declared equivalent despite having very different profiles of beneficial and adverse effects. For example, judging the global usefulness of a treatment as equivalent or superior to an alternative may mask the fact that it has little or no efficacy but fewer adverse effects. Therefore it is not advisable to use a global usefulness variable as a primary variable. If global usefulness is specified as primary, it is important to consider specific efficacy and safety outcomes separately as additional primary variables.

2.2.5 Multiple Primary Variables

It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies. The planned manner of interpretation of this type of evidence should be carefully spelled out. It should be clear whether an impact on any of the variables, some minimum number of them, or all of them, would be considered necessary to achieve the trial objectives. The primary hypothesis or hypotheses and parameters of interest (e.g. mean, percentage, distribution) should be clearly stated with respect to the primary variables identified, and the approach to statistical inference described. The effect on the type I error should be explained because of the potential for multiplicity problems (see Section 5.6); the method of controlling type I error should be given in the protocol. The extent of intercorrelation among the proposed primary variables may be considered in evaluating the impact on type I error. If the purpose of the trial is to demonstrate effects on all of the designated primary variables, then there is no need for adjustment of the type I error, but the impact on type II error and sample size should be carefully considered.

2.2.6 Surrogate Variables

When direct assessment of the clinical benefit to the subject through observing actual clinical efficacy is not practical, indirect criteria (surrogate variables - see Glossary) may be considered. Commonly accepted surrogate variables are used in a number of indications where they are believed to be reliable predictors of clinical benefit. There are two principal concerns with the introduction of any proposed surrogate variable. First, it may not be a true predictor of the clinical outcome of interest. For example it may measure treatment activity associated with one specific pharmacological mechanism, but may not provide full information on the range of actions and ultimate effects of the treatment, whether positive or negative. There have been many instances where treatments showing a highly positive effect on a proposed surrogate have ultimately been shown to be detrimental to the subjects' clinical outcome; conversely, there are cases of treatments conferring clinical benefit without measurable impact on proposed surrogates. Secondly, proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects. Statistical criteria for validating surrogate variables have been proposed but the experience with their use is relatively limited. In practice, the strength of the evidence for surrogacy depends upon (i) the biological plausibility of the relationship, (ii) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome and (iii) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome. Relationships between clinical and surrogate variables for one product do not necessarily apply to a product with a different mode of action for treating the same disease.

2.2.7 Categorised Variables

Dichotomisation or other categorisation of continuous or ordinal variables may sometimes be desirable. Criteria of 'success' and 'response' are common examples of

dichotomies which require precise specification in terms of, for example, a minimum percentage improvement (relative to baseline) in a continuous variable, or a ranking categorised as at or above some threshold level (e.g., 'good') on an ordinal rating scale. The reduction of diastolic blood pressure below 90mmHg is a common dichotomisation. Categorisations are most useful when they have clear clinical relevance. The criteria for categorisation should be pre-defined and specified in the protocol, as knowledge of trial results could easily bias the choice of such criteria. Because categorisation normally implies a loss of information, a consequence will be a loss of power in the analysis; this should be accounted for in the sample size calculation.

2.3 Design Techniques to Avoid Bias

The most important design techniques for avoiding bias in clinical trials are blinding and randomisation, and these should be normal features of most controlled clinical trials intended to be included in a marketing application. Most such trials follow a double-blind approach in which treatments are pre-packed in accordance with a suitable randomisation schedule, and supplied to the trial centre(s) labelled only with the subject number and the treatment period so that no one involved in the conduct of the trial is aware of the specific treatment allocated to any particular subject, not even as a code letter. This approach will be assumed in Section 2.3.1 and most of Section 2.3.2, exceptions being considered at the end.

Bias can also be reduced at the design stage by specifying procedures in the protocol aimed at minimising any anticipated irregularities in trial conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data.

2.3.1 Blinding

Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed.

A double-blind trial is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. This level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded. If any of the sponsor staff who are not involved in the treatment or clinical evaluation of the subjects are required to be unblinded to the treatment code (e.g. bioanalytical scientists, auditors, those involved in serious adverse event reporting), the sponsor should have adequate standard operating procedures to guard against inappropriate dissemination of treatment codes. In a single-blind trial the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa. In an open-label trial the identity of treatment is known to all. The double-blind trial is the optimal approach. This requires that the treatments to be applied during the trial cannot be distinguished (appearance, taste, etc.) either before or during administration, and that the blind is maintained appropriately during the whole trial.

Difficulties in achieving the double-blind ideal can arise: the treatments may be of a completely different nature, for example, surgery and drug therapy; two drugs may have different formulations and, although they could be made indistinguishable by the use of capsules, changing the formulation might also change the pharmacokinetic and/or pharmacodynamic properties and hence require that bioequivalence of the formulations be established; the daily pattern of administration of two treatments may differ. One way of achieving double-blind conditions under these circumstances is to use a 'double-dummy' (see Glossary) technique. This technique may sometimes force an administration scheme that is sufficiently unusual to influence adversely the motivation and compliance of the subjects. Ethical difficulties may also interfere with its use when, for example, it entails dummy operative procedures. Nevertheless, extensive efforts should be made to overcome these difficulties.

The double-blind nature of some clinical trials may be partially compromised by apparent treatment induced effects. In such cases, blinding may be improved by blinding investigators and relevant sponsor staff to certain test results (e.g. selected clinical laboratory measures). Similar approaches (see below) to minimising bias in open-label trials should be considered in trials where unique or specific treatment effects may lead to unblinding individual patients.

If a double-blind trial is not feasible, then the single-blind option should be considered. In some cases only an open-label trial is practically or ethically possible. Single-blind and open-label trials provide additional flexibility, but it is particularly important that the investigator's knowledge of the next treatment should not influence the decision to enter the subject; this decision should precede knowledge of the randomised treatment. For these trials, consideration should be given to the use of a centralised randomisation method, such as telephone randomisation, to administer the assignment of randomised treatment. In addition, clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment. In single-blind or open-label trials every effort should be made to minimise the various known sources of bias and primary variables should be as objective as possible. The reasons for the degree of blinding adopted should be explained in the protocol, together with steps taken to minimise bias by other means. For example, the sponsor should have adequate standard operating procedures to ensure that access to the treatment code is appropriately restricted during the process of cleaning the database prior to its release for analysis.

Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. The procedure and timing for revealing the treatment assignments should be documented.

In this document, the blind review (see Glossary) of data refers to the checking of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind.

2.3.2 Randomisation

Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination

with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

The randomisation schedule of a clinical trial documents the random allocation of treatments to subjects. In the simplest situation it is a sequential list of treatments (or treatment sequences in a crossover trial) or corresponding codes by subject number. The logistics of some trials, such as those with a screening phase, may make matters more complicated, but the unique pre-planned assignment of treatment, or treatment sequence, to subject should be clear. Different trial designs will require different procedures for generating randomisation schedules. The randomisation schedule should be reproducible (if the need arises).

Although unrestricted randomisation is an acceptable approach, some advantages can generally be gained by randomising subjects in blocks. This helps to increase the comparability of the treatment groups, particularly when subject characteristics may change over time, as a result, for example, of changes in recruitment policy. It also provides a better guarantee that the treatment groups will be of nearly equal size. In crossover trials it provides the means of obtaining balanced designs with their greater efficiency and easier interpretation. Care should be taken to choose block lengths that are sufficiently short to limit possible imbalance, but that are long enough to avoid predictability towards the end of the sequence in a block. Investigators and other relevant staff should generally be blind to the block length; the use of two or more block lengths, randomly selected for each block, can achieve the same purpose. (Theoretically, in a double-blind trial predictability does not matter, but the pharmacological effects of drugs may provide the opportunity for intelligent guesswork.)

In multicentre trials (see Glossary) the randomisation procedures should be organised centrally. It is advisable to have a separate random scheme for each centre, i.e. to stratify by centre or to allocate several whole blocks to each centre. More generally, stratification by important prognostic factors measured at baseline (e.g. severity of disease, age, sex, etc.) may sometimes be valuable in order to promote balanced allocation within strata; this has greater potential benefit in small trials. The use of more than two or three stratification factors is rarely necessary, is less successful at achieving balance and is logistically troublesome. The use of a dynamic allocation procedure (see below) may help to achieve balance across a number of stratification factors simultaneously provided the rest of the trial procedures can be adjusted to accommodate an approach of this type. Factors on which randomisation has been stratified should be accounted for later in the analysis.

The next subject to be randomised into a trial should always receive the treatment corresponding to the next free number in the appropriate randomisation schedule (in the respective stratum, if randomisation is stratified). The appropriate number and associated treatment for the next subject should only be allocated when entry of that subject to the randomised part of the trial has been confirmed. Details of the randomisation that facilitate predictability (e.g. block length) should not be contained in the trial protocol. The randomisation schedule itself should be filed securely by the sponsor or an independent party in a manner that ensures that blindness is properly maintained throughout the trial. Access to the randomisation schedule during the trial should take into account the possibility that, in an emergency, the blind may have to be broken for any subject. The procedure to be followed, the necessary documentation, and the subsequent treatment and assessment of the subject should all be described in the protocol.

Dynamic allocation is an alternative procedure in which the allocation of treatment to a subject is influenced by the current balance of allocated treatments and, in a

stratified trial, by the stratum to which the subject belongs and the balance within that stratum. Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation. Every effort should be made to retain the double-blind status of the trial. For example, knowledge of the treatment code may be restricted to a central trial office from where the dynamic allocation is controlled, generally through telephone contact. This in turn permits additional checks of eligibility criteria and establishes entry into the trial, features that can be valuable in certain types of multicentre trial. The usual system of pre-packing and labelling drug supplies for double-blind trials can then be followed, but the order of their use is no longer sequential. It is desirable to use appropriate computer algorithms to keep personnel at the central trial office blind to the treatment code. The complexity of the logistics and potential impact on the analysis should be carefully evaluated when considering dynamic allocation.

III. TRIAL DESIGN CONSIDERATIONS

3.1 Design Configuration

3.1.1 Parallel Group Design

The most common clinical trial design for confirmatory trials is the parallel group design in which subjects are randomised to one of two or more arms, each arm being allocated a different treatment. These treatments will include the investigational product at one or more doses, and one or more control treatments, such as placebo and/or an active comparator. The assumptions underlying this design are less complex than for most other designs. However, as with other designs, there may be additional features of the trial that complicate the analysis and interpretation (e.g. covariates, repeated measurements over time, interactions between design factors, protocol violations, dropouts (see Glossary) and withdrawals).

3.1.2 Crossover Design

In the crossover design, each subject is randomised to a sequence of two or more treatments, and hence acts as his own control for treatment comparisons. This simple manoeuvre is attractive primarily because it reduces the number of subjects and usually the number of assessments needed to achieve a specific power, sometimes to a marked extent. In the simplest 2×2 crossover design each subject receives each of two treatments in randomised order in two successive treatment periods, often separated by a washout period. The most common extension of this entails comparing n(>2) treatments in n periods, each subject receiving all n treatments. Numerous variations exist, such as designs in which each subject receives a subset of n(>2) treatments, or ones in which treatments are repeated within a subject.

Crossover designs have a number of problems that can invalidate their results. The chief difficulty concerns carryover, that is, the residual influence of treatments in subsequent treatment periods. In an additive model the effect of unequal carryover will be to bias direct treatment comparisons. In the 2×2 design the carryover effect cannot be statistically distinguished from the interaction between treatment and period and the test for either of these effects lacks power because the corresponding contrast is 'between subject'. This problem is less acute in higher order designs, but cannot be entirely dismissed.

When the crossover design is used it is therefore important to avoid carryover. This is best done by selective and careful use of the design on the basis of adequate knowledge of both the disease area and the new medication. The disease under study should be chronic and stable. The relevant effects of the medication should develop fully within the treatment period. The washout periods should be sufficiently long for

complete reversibility of drug effect. The fact that these conditions are likely to be met should be established in advance of the trial by means of prior information and data.

There are additional problems that need careful attention in crossover trials. The most notable of these are the complications of analysis and interpretation arising from the loss of subjects. Also, the potential for carryover leads to difficulties in assigning adverse events which occur in later treatment periods to the appropriate treatment. These, and other issues, are described in ICH E4. The crossover design should generally be restricted to situations where losses of subjects from the trial are expected to be small.

A common, and generally satisfactory, use of the 2×2 crossover design is to demonstrate the bioequivalence of two formulations of the same medication. In this particular application in healthy volunteers, carryover effects on the relevant pharmacokinetic variable are most unlikely to occur if the wash-out time between the two periods is sufficiently long. However it is still important to check this assumption during analysis on the basis of the data obtained, for example by demonstrating that no drug is detectable at the start of each period.

3.1.3 Factorial Designs

In a factorial design two or more treatments are evaluated simultaneously through the use of varying combinations of the treatments. The simplest example is the 2×2 factorial design in which subjects are randomly allocated to one of the four possible combinations of two treatments, A and B say. These are: A alone; B alone; both A and B; neither A nor B. In many cases this design is used for the specific purpose of examining the interaction of A and B. The statistical test of interaction may lack power to detect an interaction if the sample size was calculated based on the test for main effects. This consideration is important when this design is used for examining the joint effects of A and B, in particular, if the treatments are likely to be used together.

Another important use of the factorial design is to establish the dose-response characteristics of the simultaneous use of treatments C and D, especially when the efficacy of each monotherapy has been established at some dose in prior trials. A number, m, of doses of C is selected, usually including a zero dose (placebo), and a similar number, n, of doses of D. The full design then consists of m×n treatment groups, each receiving a different combination of doses of C and D. The resulting estimate of the response surface may then be used to help to identify an appropriate combination of doses of C and D for clinical use (see ICH E4).

In some cases, the 2×2 design may be used to make efficient use of clinical trial subjects by evaluating the efficacy of the two treatments with the same number of subjects as would be required to evaluate the efficacy of either one alone. This strategy has proved to be particularly valuable for very large mortality trials. The efficiency and validity of this approach depends upon the absence of interaction between treatments A and B so that the effects of A and B on the primary efficacy variables follow an additive model, and hence the effect of A is virtually identical whether or not it is additional to the effect of B. As for the crossover trial, evidence that this condition is likely to be met should be established in advance of the trial by means of prior information and data.

3.2 Multicentre Trials

Multicentre trials are carried out for two main reasons. Firstly, a multicentre trial is an accepted way of evaluating a new medication more efficiently; under some

circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time-frame. Multicentre trials of this nature may, in principle, be carried out at any stage of clinical development. They may have several centres with a large number of subjects per centre or, in the case of a rare disease, they may have a large number of centres with very few subjects per centre.

Secondly, a trial may be designed as a multicentre (and multi-investigator) trial primarily to provide a better basis for the subsequent generalisation of its findings. This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. In this case the involvement of a number of investigators also gives the potential for a wider range of clinical judgement concerning the value of the medication. Such a trial would be a confirmatory trial in the later phases of drug development and would be likely to involve a large number of investigators and centres. It might sometimes be conducted in a number of different countries in order to facilitate generalisability (see Glossary) even further.

If a multicentre trial is to be meaningfully interpreted and extrapolated, then the manner in which the protocol is implemented should be clear and similar at all centres. Furthermore the usual sample size and power calculations depend upon the assumption that the differences between the compared treatments in the centres are unbiased estimates of the same quantity. It is important to design the common protocol and to conduct the trial with this background in mind. Procedures should be standardised as completely as possible. Variation of evaluation criteria and schemes can be reduced by investigator meetings, by the training of personnel in advance of the trial and by careful monitoring during the trial. Good design should generally aim to achieve the same distribution of subjects to treatments within each centre and good management should maintain this design objective. Trials that avoid excessive variation in the numbers of subjects per centre and trials that avoid a few very small centres have advantages if it is later found necessary to take into account the heterogeneity of the treatment effect from centre to centre, because they reduce the differences between different weighted estimates of the treatment effect. (This point does not apply to trials in which all centres are very small and in which centre does not feature in the analysis.) Failure to take these precautions, combined with doubts about the homogeneity of the results may, in severe cases, reduce the value of a multicentre trial to such a degree that it cannot be regarded as giving convincing evidence for the sponsor's claims.

In the simplest multicentre trial, each investigator will be responsible for the subjects recruited at one hospital, so that 'centre' is identified uniquely by either investigator or hospital. In many trials, however, the situation is more complex. One investigator may recruit subjects from several hospitals; one investigator may represent a team of clinicians (subinvestigators) who all recruit subjects from their own clinics at one hospital or at several associated hospitals. Whenever there is room for doubt about the definition of centre in a statistical model, the statistical section of the protocol (see Section 5.1) should clearly define the term (e.g. by investigator, location or region) in the context of the particular trial. In most instances centres can be satisfactorily defined through the investigators and ICH E6 provides relevant guidance in this respect. In cases of doubt the aim should be to define centres so as to achieve homogeneity in the important factors affecting the measurements of the primary variables and the influence of the treatments. Any rules for combining centres in the analysis should be justified and specified prospectively in the protocol

where possible, but in any case decisions concerning this approach should always be taken blind to treatment, for example at the time of the blind review.

The statistical model to be adopted for the estimation and testing of treatment effects should be described in the protocol. The main treatment effect may be investigated first using a model which allows for centre differences, but does not include a term for treatment-by-centre interaction. If the treatment effect is homogeneous across centres, the routine inclusion of interaction terms in the model reduces the efficiency of the test for the main effects. In the presence of true heterogeneity of treatment effects, the interpretation of the main treatment effect is controversial.

In some trials, for example some large mortality trials with very few subjects per centre, there may be no reason to expect the centres to have any influence on the primary or secondary variables because they are unlikely to represent influences of clinical importance. In other trials it may be recognised from the start that the limited numbers of subjects per centre will make it impracticable to include the centre effects in the statistical model. In these cases it is not appropriate to include a term for centre in the model, and it is not necessary to stratify the randomisation by centre in this situation.

If positive treatment effects are found in a trial with appreciable numbers of subjects per centre, there should generally be an exploration of the heterogeneity of treatment effects across centres, as this may affect the generalisability of the conclusions. Marked heterogeneity may be identified by graphical display of the results of individual centres or by analytical methods, such as a significance test of the treatment-by-centre interaction. When using such a statistical significance test, it is important to recognise that this generally has low power in a trial designed to detect the main effect of treatment.

If heterogeneity of treatment effects is found, this should be interpreted with care and vigorous attempts should be made to find an explanation in terms of other features of trial management or subject characteristics. Such an explanation will usually suggest appropriate further analysis and interpretation. In the absence of an explanation, heterogeneity of treatment effect as evidenced, for example, by marked quantitative interactions (see Glossary) implies that alternative estimates of the treatment effect may be required, giving different weights to the centres, in order to substantiate the robustness of the estimates of treatment effect. It is even more important to understand the basis of any heterogeneity characterised by marked qualitative interactions (see Glossary), and failure to find an explanation may necessitate further clinical trials before the treatment effect can be reliably predicted.

Up to this point the discussion of multicentre trials has been based on the use of fixed effect models. Mixed models may also be used to explore the heterogeneity of the treatment effect. These models consider centre and treatment-by-centre effects to be random, and are especially relevant when the number of sites is large.

3.3 Type of Comparison

3.3.1 Trials to Show Superiority

Scientifically, efficacy is most convincingly established by demonstrating superiority to placebo in a placebo-controlled trial, by showing superiority to an active control treatment or by demonstrating a dose-response relationship. This type of trial is referred to as a 'superiority' trial (see Glossary). Generally in this guidance superiority trials are assumed, unless it is explicitly stated otherwise.

For serious illnesses, when a therapeutic treatment which has been shown to be efficacious by superiority trial(s) exists, a placebo-controlled trial may be considered

unethical. In that case the scientifically sound use of an active treatment as a control should be considered. The appropriateness of placebo control vs. active control should be considered on a trial by trial basis.

3.3.2 Trials to Show Equivalence or Non-inferiority

In some cases, an investigational product is compared to a reference treatment without the objective of showing superiority. This type of trial is divided into two major categories according to its objective; one is an 'equivalence' trial (see Glossary) and the other is a 'non-inferiority' trial (see Glossary).

Bioequivalence trials fall into the former category. In some situations, clinical equivalence trials are also undertaken for other regulatory reasons such as demonstrating the clinical equivalence of a generic product to the marketed product when the compound is not absorbed and therefore not present in the blood stream.

Many active control trials are designed to show that the efficacy of an investigational product is no worse than that of the active comparator, and hence fall into the latter category. Another possibility is a trial in which multiple doses of the investigational drug are compared with the recommended dose or multiple doses of the standard drug. The purpose of this design is simultaneously to show a dose-response relationship for the investigational product and to compare the investigational product with the active control.

Active control equivalence or non-inferiority trials may also incorporate a placebo, thus pursuing multiple goals in one trial; for example, they may establish superiority to placebo and hence validate the trial design and simultaneously evaluate the degree of similarity of efficacy and safety to the active comparator. There are well known difficulties associated with the use of the active control equivalence (or non-inferiority) trials that do not incorporate a placebo or do not use multiple doses of the new drug. These relate to the implicit lack of any measure of internal validity (in contrast to superiority trials), thus making external validation necessary. The equivalence (or non-inferiority) trial is not conservative in nature, so that many flaws in the design or conduct of the trial will tend to bias the results towards a conclusion of equivalence. For these reasons, the design features of such trials should receive special attention and their conduct needs special care. For example, it is especially important to minimise the incidence of violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol, and also to minimise their impact on the subsequent analyses.

Active comparators should be chosen with care. An example of a suitable active comparator would be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well designed and well documented superiority trial(s) and which can be reliably expected to exhibit similar efficacy in the contemplated active control trial. To this end, the new trial should have the same important design features (primary variables, the dose of the active comparator, eligibility criteria, etc.) as the previously conducted superiority trials in which the active comparator clearly demonstrated clinically relevant efficacy, taking into account advances in medical or statistical practice relevant to the new trial.

It is vital that the protocol of a trial designed to demonstrate equivalence or non-inferiority contain a clear statement that this is its explicit intention. An equivalence margin should be specified in the protocol; this margin is the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator. For the active control equivalence trial, both the upper and the lower equivalence margins are needed,

while only the lower margin is needed for the active control non-inferiority trial. The choice of equivalence margins should be justified clinically.

Statistical analysis is generally based on the use of confidence intervals (see Section 5.5). For equivalence trials, two-sided confidence intervals should be used. Equivalence is inferred when the entire confidence interval falls within the equivalence margins. Operationally, this is equivalent to the method of using two simultaneous one-sided tests to test the (composite) null hypothesis that the treatment difference is outside the equivalence margins versus the (composite) alternative hypothesis that the treatment difference is within the margins. Because the two null hypotheses are disjoint, the type I error is appropriately controlled. For non-inferiority trials a one-sided interval should be used. The confidence interval approach has a one-sided hypothesis test counterpart for testing the null hypothesis that the treatment difference (investigational product minus control) is equal to the lower equivalence margin versus the alternative that the treatment difference is greater than the lower equivalence margin. The choice of type I error should be a consideration separate from the use of a one-sided or two-sided procedure. Sample size calculations should be based on these methods (see Section 3.5).

Concluding equivalence or non-inferiority based on observing a non-significant test result of the null hypothesis that there is no difference between the investigational product and the active comparator is inappropriate.

There are also special issues in the choice of analysis sets. Subjects who withdraw or dropout of the treatment group or the comparator group will tend to have a lack of response, and hence the results of using the full analysis set (see Glossary) may be biased toward demonstrating equivalence (see Section 5.2.3).

3.3.3 Trials to Show Dose-response Relationship

How response is related to the dose of a new investigational product is a question to which answers may be obtained in all phases of development, and by a variety of approaches (see ICH E4). Dose-response trials may serve a number of objectives, amongst which the following are of particular importance: the confirmation of efficacy; the investigation of the shape and location of the dose-response curve; the estimation of an appropriate starting dose; the identification of optimal strategies for individual dose adjustments; the determination of a maximal dose beyond which additional benefit would be unlikely to occur. These objectives should be addressed using the data collected at a number of doses under investigation, including a placebo (zero dose) wherever appropriate. For this purpose the application of procedures to estimate the relationship between dose and response, including the construction of confidence intervals and the use of graphical methods, is as important as the use of statistical tests. The hypothesis tests that are used may need to be tailored to the natural ordering of doses or to particular questions regarding the shape of the dose-response curve (e.g. monotonicity). The details of the planned statistical procedures should be given in the protocol.

3.4 Group Sequential Designs

Group sequential designs are used to facilitate the conduct of interim analysis (see section 4.5 and Glossary). While group sequential designs are not the only acceptable types of designs permitting interim analysis, they are the most commonly applied because it is more practicable to assess grouped subject outcomes at periodic intervals during the trial than on a continuous basis as data from each subject become available. The statistical methods should be fully specified in advance of the availability of information on treatment outcomes and subject treatment assignments (i.e. blind breaking, see Section 4.5). An Independent Data Monitoring Committee

(see Glossary) may be used to review or to conduct the interim analysis of data arising from a group sequential design (see Section 4.6). While the design has been most widely and successfully used in large, long-term trials of mortality or major non-fatal endpoints, its use is growing in other circumstances. In particular, it is recognised that safety must be monitored in all trials and therefore the need for formal procedures to cover early stopping for safety reasons should always be considered.

3.5 Sample Size

The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified. For example, a trial sized on the basis of safety questions or requirements or important secondary objectives may need larger numbers of subjects than a trial sized on the basis of the primary efficacy question (see, for example, ICH E1a).

Using the usual method for determining the appropriate sample size, the following items should be specified: a primary variable, the test statistic, the null hypothesis, the alternative ('working') hypothesis at the chosen dose(s) (embodying consideration of the treatment difference to be detected or rejected at the dose and in the subject population selected), the probability of erroneously rejecting the null hypothesis (the type I error), and the probability of erroneously failing to reject the null hypothesis (the type II error), as well as the approach to dealing with treatment withdrawals and protocol violations. In some instances, the event rate is of primary interest for evaluating power, and assumptions should be made to extrapolate from the required number of events to the eventual sample size for the trial.

The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected). The basis of these estimates should also be given. It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions. In confirmatory trials, assumptions should normally be based on published data or on the results of earlier trials. The treatment difference to be detected may be based on a judgement concerning the minimal effect which has clinical relevance in the management of patients or on a judgement concerning the anticipated effect of the new treatment, where this is larger. Conventionally the probability of type I error is set at 5% or less or as dictated by any adjustments made necessary for multiplicity considerations; the precise choice may be influenced by the prior plausibility of the hypothesis under test and the desired impact of the results. The probability of type II error is conventionally set at 10% to 20%; it is in the sponsor's interest to keep this figure as low as feasible especially in the case of trials that are difficult or impossible to repeat. Alternative values to the conventional levels of type I and type II error may be acceptable or even preferable in some cases.

Sample size calculations should refer to the number of subjects required for the primary analysis. If this is the 'full analysis set', estimates of the effect size may need to be reduced compared to the per protocol set (see Glossary). This is to allow for the dilution of the treatment effect arising from the inclusion of data from patients who have withdrawn from treatment or whose compliance is poor. The assumptions about variability may also need to be revised.

The sample size of an equivalence trial or a non-inferiority trial (see Section 3.3.2) should normally be based on the objective of obtaining a confidence interval for the treatment difference that shows that the treatments differ at most by a clinically acceptable difference. When the power of an equivalence trial is assessed at a true difference of zero, then the sample size necessary to achieve this power is underestimated if the true difference is not zero. When the power of a non-inferiority trial is assessed at a zero difference, then the sample size needed to achieve that power will be underestimated if the effect of the investigational product is less than that of the active control. The choice of a 'clinically acceptable' difference needs justification with respect to its meaning for future patients, and may be smaller than the 'clinically relevant' difference referred to above in the context of superiority trials designed to establish that a difference exists.

The exact sample size in a group sequential trial cannot be fixed in advance because it depends upon the play of chance in combination with the chosen stopping guideline and the true treatment difference. The design of the stopping guideline should take into account the consequent distribution of the sample size, usually embodied in the expected and maximum sample sizes.

When event rates are lower than anticipated or variability is larger than expected, methods for sample size re-estimation are available without unblinding data or making treatment comparisons (see Section 4.4).

3.6 Data Capture and Processing

The collection of data and transfer of data from the investigator to the sponsor can take place through a variety of media, including paper case record forms, remote site monitoring systems, medical computer systems and electronic transfer. Whatever data capture instrument is used, the form and content of the information collected should be in full accordance with the protocol and should be established in advance of the conduct of the clinical trial. It should focus on the data necessary to implement the planned analysis, including the context information (such as timing assessments relative to dosing) necessary to confirm protocol compliance or identify important protocol deviations. 'Missing values' should be distinguishable from the 'value zero' or 'characteristic absent'.

The process of data capture through to database finalisation should be carried out in accordance with GCP (see ICH E6, Section 5). Specifically, timely and reliable processes for recording data and rectifying errors and omissions are necessary to ensure delivery of a quality database and the achievement of the trial objectives through the implementation of the planned analysis.

IV. TRIAL CONDUCT CONSIDERATIONS

4.1 Trial Monitoring and Interim Analysis

Careful conduct of a clinical trial according to the protocol has a major impact on the credibility of the results (see ICH E6). Careful monitoring can ensure that difficulties are noticed early and their occurrence or recurrence minimised.

There are two distinct types of monitoring that generally characterise confirmatory clinical trials sponsored by the pharmaceutical industry. One type of monitoring concerns the oversight of the quality of the trial, while the other type involves breaking the blind to make treatment comparisons (i.e. interim analysis). Both types of trial monitoring, in addition to entailing different staff responsibilities, involve access to different types of trial data and information, and thus different principles apply for the control of potential statistical and operational bias.

For the purpose of overseeing the quality of the trial the checks involved in trial monitoring may include whether the protocol is being followed, the acceptability of data being accrued, the success of planned accrual targets, the appropriateness of the design assumptions, success in keeping patients in the trials, etc. (see Sections 4.2 to 4.4). This type of monitoring does not require access to information on comparative treatment effects, nor unblinding of data and therefore has no impact on type I error. The monitoring of a trial for this purpose is the responsibility of the sponsor (see ICH E6) and can be carried out by the sponsor or an independent group selected by the sponsor. The period for this type of monitoring usually starts with the selection of the trial sites and ends with the collection and cleaning of the last subject's data.

The other type of trial monitoring (interim analysis) involves the accruing of comparative treatment results. Interim analysis requires unblinded (i.e. key breaking) access to treatment group assignment (actual treatment assignment or identification of group assignment) and comparative treatment group summary information. This necessitates that the protocol (or appropriate amendments prior to a first analysis) contains statistical plans for the interim analysis to prevent certain types of bias. This is discussed in Sections 4.5 & 4.6.

4.2 Changes in Inclusion and Exclusion Criteria

Inclusion and exclusion criteria should remain constant, as specified in the protocol, throughout the period of subject recruitment. Changes may occasionally be appropriate, for example, in long term trials, where growing medical knowledge either from outside the trial or from interim analyses may suggest a change of entry criteria. Changes may also result from the discovery by monitoring staff that regular violations of the entry criteria are occurring, or that seriously low recruitment rates are due to over-restrictive criteria. Changes should be made without breaking the blind and should always be described by a protocol amendment which should cover any statistical consequences, such as sample size adjustments arising from different event rates, or modifications to the planned analysis, such as stratifying the analysis according to modified inclusion/exclusion criteria.

4.3 Accrual Rates

In trials with a long time-scale for the accrual of subjects, the rate of accrual should be monitored and, if it falls appreciably below the projected level, the reasons should be identified and remedial actions taken in order to protect the power of the trial and alleviate concerns about selective entry and other aspects of quality. In a multicentre trial these considerations apply to the individual centres.

4.4 Sample Size Adjustment

In long term trials there will usually be an opportunity to check the assumptions which underlay the original design and sample size calculations. This may be particularly important if the trial specifications have been made on preliminary and/or uncertain information. An interim check conducted on the blinded data may reveal that overall response variances, event rates or survival experience are not as anticipated. A revised sample size may then be calculated using suitably modified assumptions, and should be justified and documented in a protocol amendment and in the clinical study report. The steps taken to preserve blindness and the consequences, if any, for the type I error and the width of confidence intervals should be explained. The potential need for re-estimation of the sample size should be envisaged in the protocol whenever possible (see Section 3.5).

4.5 Interim Analysis and Early Stopping

An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial. Because the number, methods and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol. Special circumstances may dictate the need for an interim analysis that was not defined at the start of a trial. In these cases, a protocol amendment describing the interim analysis should be completed prior to unblinded access to treatment comparison data. When an interim analysis is planned with the intention of deciding whether or not to terminate a trial, this is usually accomplished by the use of a group sequential design which employs statistical monitoring schemes as guidelines (see Section 3.4). The goal of such an interim analysis is to stop the trial early if the superiority of the treatment under study is clearly established, if the demonstration of a relevant treatment difference has become unlikely or if unacceptable adverse effects are apparent. Generally, boundaries for monitoring efficacy require more evidence to terminate a trial early (i.e. they are more conservative) than boundaries for monitoring safety. When the trial design and monitoring objective involve multiple endpoints then this aspect of multiplicity may also need to be taken into account.

The protocol should describe the schedule of interim analyses, or at least the considerations which will govern its generation, for example if flexible alpha spending function approaches are to be employed; further details may be given in a protocol amendment before the time of the first interim analysis. The stopping guidelines and their properties should be clearly described in the protocol or amendments. The potential effects of early stopping on the analysis of other important variables should also be considered. This material should be written or approved by the Data Monitoring Committee (see Section 4.6), when the trial has one. Deviations from the planned procedure always bear the potential of invalidating the trial results. If it becomes necessary to make changes to the trial, any consequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis and inferences that such changes may cause. The procedures selected should always ensure that the overall probability of type I error is controlled.

The execution of an interim analysis should be a completely confidential process because unblinded data and results are potentially involved. All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the interim analysis. Investigators should only be informed about the decision to continue or to discontinue the trial, or to implement modifications to trial procedures.

Most clinical trials intended to support the efficacy and safety of an investigational product should proceed to full completion of planned sample size accrual; trials should be stopped early only for ethical reasons or if the power is no longer acceptable. However, it is recognised that drug development plans involve the need for sponsor access to comparative treatment data for a variety of reasons, such as planning other trials. It is also recognised that only a subset of trials will involve the study of serious life-threatening outcomes or mortality which may need sequential monitoring of accruing comparative treatment effects for ethical reasons. In either of these situations, plans for interim statistical analysis should be in place in the protocol or in protocol amendments prior to the unblinded access to comparative

treatment data in order to deal with the potential statistical and operational bias that may be introduced.

For many clinical trials of investigational products, especially those that have major public health significance, the responsibility for monitoring comparisons of efficacy and/or safety outcomes should be assigned to an external independent group, often called an Independent Data Monitoring Committee (IDMC), a Data and Safety Monitoring Board or a Data Monitoring Committee whose responsibilities should be clearly described.

When a sponsor assumes the role of monitoring efficacy or safety comparisons and therefore has access to unblinded comparative information, particular care should be taken to protect the integrity of the trial and to manage and limit appropriately the sharing of information. The sponsor should assure and document that the internal monitoring committee has complied with written standard operating procedures and that minutes of decision making meetings including records of interim results are maintained.

Any interim analysis that is not planned appropriately (with or without the consequences of stopping the trial early) may flaw the results of a trial and possibly weaken confidence in the conclusions drawn. Therefore, such analyses should be avoided. If unplanned interim analysis is conducted, the clinical study report should explain why it was necessary, the degree to which blindness had to be broken, provide an assessment of the potential magnitude of bias introduced, and the impact on the interpretation of the results.

4.6 Role of Independent Data Monitoring Committee (IDMC) (see Sections 1.25 and 5.52 of ICH E6)

An IDMC may be established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The IDMC should have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The IDMC is a separate entity from an Institutional Review Board (IRB) or an Independent Ethics Committee (IEC), and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines including statistics.

When there are sponsor representatives on the IDMC, their role should be clearly defined in the operating procedures of the committee (for example, covering whether or not they can vote on key issues). Since these sponsor staff would have access to unblinded information, the procedures should also address the control of dissemination of interim trial results within the sponsor organisation.

V. DATA ANALYSIS CONSIDERATIONS

5.1 Prespecification of the Analysis

When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol. This section should include all the principal features of the proposed confirmatory analysis of the primary variable(s) and the way in which anticipated analysis problems will be handled. In case of exploratory trials this section could describe more general principles and directions.

The statistical analysis plan (see Glossary) may be written as a separate document to be completed after finalising the protocol. In this document, a more technical and detailed elaboration of the principal features stated in the protocol may be included (see section 7.1). The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of the data (see 7.1 for definition) and should be finalised before breaking the blind. Formal records should be kept of when the statistical analysis plan was finalised as well as when the blind was subsequently broken.

If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review. Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

In the statistical section of the clinical study report the statistical methodology should be clearly described including when in the clinical trial process methodology decisions were made (see ICH E3).

5.2 Analysis Sets

The set of subjects whose data are to be included in the main analyses should be defined in the statistical section of the protocol. In addition, documentation for all subjects for whom trial procedures (e.g. run-in period) were initiated may be useful. The content of this subject documentation depends on detailed features of the particular trial, but at least demographic and baseline data on disease status should be collected whenever possible.

If all subjects randomised into a clinical trial satisfied all entry criteria, followed all trial procedures perfectly with no losses to follow-up, and provided complete data records, then the set of subjects to be included in the analysis would be self-evident. The design and conduct of a trial should aim to approach this ideal as closely as possible, but, in practice, it is doubtful if it can ever be fully achieved. Hence, the statistical section of the protocol should address anticipated problems prospectively in terms of how these affect the subjects and data to be analysed. The protocol should also specify procedures aimed at minimising any anticipated irregularities in study conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data. Possible amendments to the way in which the analysis will deal with protocol violations should be identified during the blind review. It is desirable to identify any important protocol violation with respect to the time when it occurred, its cause and influence on the trial result. The frequency and type of protocol violations, missing values, and other problems should be documented in the clinical study report and their potential influence on the trial results should be described (see ICH E3).

Decisions concerning the analysis set should be guided by the following principles : 1) to minimise bias, and 2) to avoid inflation of type I error.

5.2.1 Full Analysis Set

The intention-to-treat (see Glossary) principle implies that the primary analysis should include all randomised subjects. Compliance with this principle would necessitate complete follow-up of all randomised subjects for study outcomes. In practice this ideal may be difficult to achieve, for reasons to be described. In this

document the term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects. Preservation of the initial randomisation in analysis is important in preventing bias and in providing a secure foundation for statistical tests. In many clinical trials the use of the full analysis set provides a conservative strategy. Under many circumstances it may also provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice.

There are a limited number of circumstances that might lead to excluding randomised subjects from the full analysis set including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication and the lack of any data post randomisation. Such exclusions should always be justified. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

(i) the entry criterion was measured prior to randomisation;

(ii) the detection of the relevant eligibility violations can be made completely objectively;

(iii) all subjects receive equal scrutiny for eligibility violations; (This may be difficult to ensure in an open-label study, or even in a double-blind study if the data are unblinded prior to this scrutiny, emphasising the importance of the blind review.)

(iv) all detected violations of the particular entry criterion are excluded.

In some situations, it may be reasonable to eliminate from the set of all randomised subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment. In other situations it may be necessary to eliminate from the set of all randomised subjects any subject without data post randomisation. No analysis is complete unless the potential biases arising from these specific exclusions, or any others, are addressed.

When the full analysis set of subjects is used, violations of the protocol that occur after randomisation may have an impact on the data and conclusions, particularly if their occurrence is related to treatment assignment. In most respects it is appropriate to include the data from such subjects in the analysis, consistent with the intention-to-treat principle. Special problems arise in connection with subjects withdrawn from treatment after receiving one or more doses who provide no data after this point, and subjects otherwise lost to follow-up, because failure to include these subjects in the full analysis set may seriously undermine the approach. Measurements of primary variables made at the time of the loss to follow-up of a subject for any reason, or subsequently collected in accordance with the intended schedule of assessments in the protocol, are valuable in this context; subsequent collection is especially important in studies where the primary variable is mortality or serious morbidity. The intention to collect data in this way should be described in the protocol. Imputation techniques, ranging from the carrying forward of the last observation to the use of complex mathematical models, may also be used in an attempt to compensate for missing data. Other methods employed to ensure the availability of measurements of primary variables for every subject in the full analysis set may require some assumptions about the subjects' outcomes or a simpler

choice of outcome (e.g. success / failure). The use of any of these strategies should be described and justified in the statistical section of the protocol and the assumptions underlying any mathematical models employed should be clearly explained. It is also important to demonstrate the robustness of the corresponding results of analysis especially when the strategy in question could itself lead to biased estimates of treatment effects.

Because of the unpredictability of some problems, it may sometimes be preferable to defer detailed consideration of the manner of dealing with irregularities until the blind review of the data at the end of the trial, and, if so, this should be stated in the protocol.

5.2.2 Per Protocol Set

The 'per protocol' set of subjects, sometimes described as the 'valid cases', the 'efficacy' sample or the 'evaluable subjects' sample, defines a subset of the subjects in the full analysis set who are more compliant with the protocol and is characterised by criteria such as the following:

(i) the completion of a certain pre-specified minimal exposure to the treatment regimen;

(ii) the availability of measurements of the primary variable(s);

(iii) the absence of any major protocol violations including the violation of entry criteria.

The precise reasons for excluding subjects from the per protocol set should be fully defined and documented before breaking the blind in a manner appropriate to the circumstances of the specific trial.

The use of the per protocol set may maximise the opportunity for a new treatment to show additional efficacy in the analysis, and most closely reflects the scientific model underlying the protocol. However, the corresponding test of the hypothesis and estimate of the treatment effect may or may not be conservative depending on the trial; the bias, which may be severe, arises from the fact that adherence to the study protocol may be related to treatment and outcome.

The problems that lead to the exclusion of subjects to create the per protocol set, and other protocol violations, should be fully identified and summarised. Relevant protocol violations may include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data. It is good practice to assess the pattern of such problems among the treatment groups with respect to frequency and time to occurrence.

5.2.3 Roles of the Different Analysis Sets

In general, it is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of the set of subjects analysed. In confirmatory trials it is usually appropriate to plan to conduct both an analysis of the full analysis set and a per protocol analysis, so that any differences between them can be the subject of explicit discussion and interpretation. In some cases, it may be desirable to plan further exploration of the sensitivity of conclusions to the choice of the set of subjects analysed. When the full analysis set and the per protocol set lead to essentially the same conclusions, confidence in the trial results is increased, bearing in mind, however, that the need to exclude a substantial proportion of subjects from the per protocol analysis throws some doubt on the overall validity of the trial.

The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior), and in equivalence or non-inferiority trials (which seek to show the investigational product to be comparable, see section 3.3.2). In superiority trials the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis, since the non-compliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully.

5.3 Missing Values and Outliers

Missing values represent a potential source of bias in a clinical trial. Hence, every effort should be undertaken to fulfil all the requirements of the protocol concerning the collection and management of data. In reality, however, there will almost always be some missing data. A trial may be regarded as valid, nonetheless, provided the methods of dealing with missing values are sensible, and particularly if those methods are pre-defined in the protocol. Definition of methods may be refined by updating this aspect in the statistical analysis plan during the blind review. Unfortunately, no universally applicable methods of handling missing values can be recommended. An investigation should be made concerning the sensitivity of the results of analysis to the method of handling missing values, especially if the number of missing values is substantial.

A similar approach should be adopted to exploring the influence of outliers, the statistical definition of which is, to some extent, arbitrary. Clear identification of a particular value as an outlier is most convincing when justified medically as well as statistically, and the medical context will then often define the appropriate action. Any outlier procedure set out in the protocol or the statistical analysis plan should be such as not to favour any treatment group a priori. Once again, this aspect of the analysis can be usefully updated during blind review. If no procedure for dealing with outliers was foreseen in the trial protocol, one analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect should be performed and differences between their results discussed.

5.4 Data Transformation

The decision to transform key variables prior to analysis is best made during the design of the trial on the basis of similar data from earlier clinical trials. Transformations (e.g. square root, logarithm) should be specified in the protocol and a rationale provided, especially for the primary variable(s). The general principles guiding the use of transformations to ensure that the assumptions underlying the statistical methods are met are to be found in standard texts; conventions for particular variables have been developed in a number of specific clinical areas. The decision on whether and how to transform a variable should be influenced by the preference for a scale which facilitates clinical interpretation.

Similar considerations apply to other derived variables, such as the use of change from baseline, percentage change from baseline, the 'area under the curve' of repeated measures, or the ratio of two different variables. Subsequent clinical interpretation should be carefully considered, and the derivation should be justified in the protocol. Closely related points are made in Section 2.2.2.

5.5 Estimation, Confidence Intervals and Hypothesis Testing

The statistical section of the protocol should specify the hypotheses that are to be tested and/or the treatment effects which are to be estimated in order to satisfy the primary objectives of the trial. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables, and the underlying statistical model should be made clear. Estimates of treatment effects should be accompanied by confidence intervals, whenever possible, and the way in which these will be calculated should be identified. A description should be given of any intentions to use baseline data to improve precision or to adjust estimates for potential baseline differences, for example by means of analysis of covariance.

It is important to clarify whether one- or two-sided tests of statistical significance will be used, and in particular to justify prospectively the use of one-sided tests. If hypothesis tests are not considered appropriate, then the alternative process for arriving at statistical conclusions should be given. The issue of one-sided or two-sided approaches to inference is controversial and a diversity of views can be found in the statistical literature. The approach of setting type I errors for one-sided tests at half the conventional type I error used in two-sided tests is preferable in regulatory settings. This promotes consistency with the two-sided confidence intervals that are generally appropriate for estimating the possible size of the difference between two treatments.

The particular statistical model chosen should reflect the current state of medical and statistical knowledge about the variables to be analysed as well as the statistical design of the trial. All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified, and the manner, if any, in which this set of effects might be modified in response to preliminary results should be explained. The same considerations apply to the set of covariates fitted in an analysis of covariance. (See also Section 5.7.). In the choice of statistical methods due attention should be paid to the statistical distribution of both primary and secondary variables. When making this choice (for example between parametric and non-parametric methods) it is important to bear in mind the need to provide statistical estimates of the size of treatment effects together with confidence intervals (in addition to significance tests).

The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables. Within the statistical section of the protocol or the statistical analysis plan there should also be an outline of the way in which data other than the primary and secondary variables will be summarised and reported. This should include a reference to any approaches adopted for the purpose of achieving consistency of analysis across a range of trials, for example for safety data.

Modelling approaches that incorporate information on known pharmacological parameters, the extent of protocol compliance for individual subjects or other biologically based data may provide valuable insights into actual or potential efficacy, especially with regard to estimation of treatment effects. The assumptions underlying such models should always be clearly identified, and the limitations of any conclusions should be carefully described.

5.6 Adjustment of Significance and Confidence Levels

When multiplicity is present, the usual frequentist approach to the analysis of clinical trial data may necessitate an adjustment to the type I error. Multiplicity may arise, for example, from multiple primary variables (see Section 2.2.2), multiple comparisons of treatments, repeated evaluation over time and/or interim analyses (see Section 4.5). Methods to avoid or reduce multiplicity are sometimes preferable

when available, such as the identification of the key primary variable (multiple variables), the choice of a critical treatment contrast (multiple comparisons), the use of a summary measure such as 'area under the curve' (repeated measures). In confirmatory analyses, any aspects of multiplicity which remain after steps of this kind have been taken should be identified in the protocol; adjustment should always be considered and the details of any adjustment procedure or an explanation of why adjustment is not thought to be necessary should be set out in the analysis plan.

5.7 Subgroups, Interactions and Covariates

The primary variable(s) is often systematically related to other influences apart from treatment. For example, there may be relationships to covariates such as age and sex, or there may be differences between specific subgroups of subjects such as those treated at the different centres of a multicentre trial. In some instances an adjustment for the influence of covariates or for subgroup effects is an integral part of the planned analysis and hence should be set out in the protocol. Pre-trial deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis in order to improve precision and to compensate for any lack of balance between treatment groups. If one or more factors are used to stratify the design, it is appropriate to account for those factors in the analysis. When the potential value of an adjustment is in doubt, it is often advisable to nominate the unadjusted analysis as the one for primary attention, the adjusted analysis being supportive. Special attention should be paid to centre effects and to the role of baseline measurements of the primary variable. It is not advisable to adjust the main analyses for covariates measured after randomisation because they may be affected by the treatments.

The treatment effect itself may also vary with subgroup or covariate - for example, the effect may decrease with age or may be larger in a particular diagnostic category of subjects. In some cases such interactions are anticipated or are of particular prior interest (e.g. geriatrics), and hence a subgroup analysis, or a statistical model including interactions, is part of the planned confirmatory analysis. In most cases, however, subgroup or interaction analyses are exploratory and should be clearly identified as such; they should explore the uniformity of any treatment effects found overall. In general, such analyses should proceed first through the addition of interaction terms to the statistical model in question, complemented by additional exploratory analysis within relevant subgroups of subjects, or within strata defined by the covariates. When exploratory, these analyses should be interpreted cautiously; any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted.

5.8 Integrity of Data and Computer Software Validity

The credibility of the numerical results of the analysis depends on the quality and validity of the methods and software (both internally and externally written) used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. Data management activities should therefore be based on thorough and effective standard operating procedures. The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available.

VI. EVALUATION OF SAFETY AND TOLERABILITY

6.1 Scope of Evaluation

In all clinical trials evaluation of safety and tolerability (see Glossary) constitutes an important element. In early phases this evaluation is mostly of an exploratory nature, and is only sensitive to frank expressions of toxicity, whereas in later phases the establishment of the safety and tolerability profile of a drug can be characterised more fully in larger samples of subjects. Later phase controlled trials represent an important means of exploring in an unbiased manner any new potential adverse effects, even if such trials generally lack power in this respect.

Certain trials may be designed with the purpose of making specific claims about superiority or equivalence with regard to safety and tolerability compared to another drug or to another dose of the investigational drug. Such specific claims should be supported by relevant evidence from confirmatory trials, similar to that necessary for corresponding efficacy claims.

6.2 Choice of Variables and Data Collection

In any clinical trial the methods and measurements chosen to evaluate the safety and tolerability of a drug will depend on a number of factors, including knowledge of the adverse effects of closely related drugs, information from non-clinical and earlier clinical trials and possible consequences of the pharmacodynamic/pharmacokinetic properties of the particular drug, the mode of administration, the type of subjects to be studied, and the duration of the trial. Laboratory tests concerning clinical chemistry and haematology, vital signs, and clinical adverse events (diseases, signs and symptoms) usually form the main body of the safety and tolerability data. The occurrence of serious adverse events and treatment discontinuations due to adverse events are particularly important to register (see ICH E2A and ICH E3).

Furthermore, it is recommended that a consistent methodology be used for the data collection and evaluation throughout a clinical trial program in order to facilitate the combining of data from different trials. The use of a common adverse event dictionary is particularly important. This dictionary has a structure which gives the possibility to summarise the adverse event data on three different levels; system-organ class, preferred term or included term (see Glossary). The preferred term is the level on which adverse events usually are summarised, and preferred terms belonging to the same system-organ class could then be brought together in the descriptive presentation of data (see ICH M1).

6.3 Set of Subjects to be Evaluated and Presentation of Data

For the overall safety and tolerability assessment, the set of subjects to be summarised is usually defined as those subjects who received at least one dose of the investigational drug. Safety and tolerability variables should be collected as comprehensively as possible from these subjects, including type of adverse event, severity, onset and duration (see ICH E2B). Additional safety and tolerability evaluations may be needed in specific subpopulations, such as females, the elderly (see ICH E7), the severely ill, or those who have a common concomitant treatment. These evaluations may need to address more specific issues (see ICH E3).

All safety and tolerability variables will need attention during evaluation, and the broad approach should be indicated in the protocol. All adverse events should be reported, whether or not they are considered to be related to treatment. All available data in the study population should be accounted for in the evaluation. Definitions of measurement units and reference ranges of laboratory variables should be made with care; if different units or different reference ranges appear in the same trial (e.g. if more than one laboratory is involved), then measurements should be appropriately standardised to allow a unified evaluation. Use of a toxicity grading scale should be prespecified and justified.

The incidence of a certain adverse event is usually expressed in the form of a proportion relating number of subjects experiencing events to number of subjects at risk. However, it is not always self-evident how to assess incidence. For example, depending on the situation the number of exposed subjects or the extent of exposure (in person-years) could be considered for the denominator. Whether the purpose of the calculation is to estimate a risk or to make a comparison between treatment groups it is important that the definition is given in the protocol. This is especially important if long-term treatment is planned and a substantial proportion of treatment withdrawals or deaths are expected. For such situations survival analysis methods should be considered and cumulative adverse event rates calculated in order to avoid the risk of underestimation.

In situations when there is a substantial background noise of signs and symptoms (e.g. in psychiatric trials) one should consider ways of accounting for this in the estimation of risk for different adverse events. One such method is to make use of the 'treatment emergent' (see Glossary) concept in which adverse events are recorded only if they emerge or worsen relative to pretreatment baseline.

Other methods to reduce the effect of the background noise may also be appropriate such as ignoring adverse events of mild severity or requiring that an event should have been observed at repeated visits to qualify for inclusion in the numerator. Such methods should be explained and justified in the protocol.

6.4 Statistical Evaluation

The investigation of safety and tolerability is a multidimensional problem. Although some specific adverse effects can usually be anticipated and specifically monitored for any drug, the range of possible adverse effects is very large, and new and unforeseeable effects are always possible. Further, an adverse event experienced after a protocol violation, such as use of an excluded medication, may introduce a bias. This background underlies the statistical difficulties associated with the analytical evaluation of safety and tolerability of drugs, and means that conclusive information from confirmatory clinical trials is the exception rather than the rule.

In most trials the safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation. It is also valuable to make use of graphical presentations in which patterns of adverse events are displayed both within treatment groups and within subjects.

The calculation of p-values is sometimes useful either as an aid to evaluating a specific difference of interest, or as a 'flagging' device applied to a large number of safety and tolerability variables to highlight differences worth further attention. This is particularly useful for laboratory data, which otherwise can be difficult to summarise appropriately. It is recommended that laboratory data be subjected to both a quantitative analysis, e.g. evaluation of treatment means, and a qualitative analysis where counting of numbers above or below certain thresholds are calculated.

If hypothesis tests are used, statistical adjustments for multiplicity to quantify the type I error are appropriate, but the type II error is usually of more concern. Care should be taken when interpreting putative statistically significant findings when there is no multiplicity adjustment.

In the majority of trials investigators are seeking to establish that there are no clinically unacceptable differences in safety and tolerability compared with either a comparator drug or a placebo. As is the case for non-inferiority or equivalence evaluation of efficacy the use of confidence intervals is preferred to hypothesis testing

in this situation. In this way, the considerable imprecision often arising from low frequencies of occurrence is clearly demonstrated.

6.5 Integrated Summary

The safety and tolerability properties of a drug are commonly summarised across trials continuously during an investigational product's development and in particular at the time of a marketing application. The usefulness of this summary, however, is dependent on adequate and well-controlled individual trials with high data quality.

The overall usefulness of a drug is always a question of balance between risk and benefit and in a single trial such a perspective could also be considered, even if the assessment of risk/benefit usually is performed in the summary of the entire clinical trial program. (See section 7.2.2)

For more details on the reporting of safety and tolerability, see Chapter 12 of ICH E3.

VII. REPORTING

7.1 Evaluation and Reporting

As stated in the Introduction, the structure and content of clinical study reports is the subject of ICH E3. That ICH guidance fully covers the reporting of statistical work, appropriately integrated with clinical and other material. The current section is therefore relatively brief.

During the planning phase of a trial the principal features of the analysis should have been specified in the protocol as described in Section 5. When the conduct of the trial is over and the data are assembled and available for preliminary inspection, it is valuable to carry out the blind review of the planned analysis also described in Section 5. This pre-analysis review, blinded to treatment, should cover decisions concerning, for example, the exclusion of subjects or data from the analysis sets; possible transformations may also be checked, and outliers defined; important covariates identified in other recent research may be added to the model; the use of parametric or non-parametric methods may be reconsidered. Decisions made at this time should be described in the report, and should be distinguished from those made after the statistician has had access to the treatment codes, as blind decisions will generally introduce less potential for bias. Statisticians or other staff involved in unblinded interim analysis should not participate in the blind review or in making modifications to the statistical analysis plan. When the blinding is compromised by the possibility that treatment induced effects may be apparent in the data, special care will be needed for the blind review.

Many of the more detailed aspects of presentation and tabulation should be finalised at or about the time of the blind review so that by the time of the actual analysis full plans exist for all its aspects including subject selection, data selection and modification, data summary and tabulation, estimation and hypothesis testing. Once data validation is complete, the analysis should proceed according to the pre-defined plans; the more these plans are adhered to, the greater the credibility of the results. Particular attention should be paid to any differences between the planned analysis and the actual analysis as described in the protocol, protocol amendments or the updated statistical analysis plan based on a blind review of data. A careful explanation should be provided for deviations from the planned analysis.

All subjects who entered the trial should be accounted for in the report, whether or not they are included in the analysis. All reasons for exclusion from analysis should be documented; for any subject included in the full analysis set but not in the per protocol set, the reasons for exclusion from the latter should also be documented.

Similarly, for all subjects included in an analysis set, the measurements of all important variables should be accounted for at all relevant time-points.

The effect of all losses of subjects or data, withdrawals from treatment and major protocol violations on the main analyses of the primary variable(s) should be considered carefully. Subjects lost to follow up, withdrawn from treatment, or with a severe protocol violation should be identified, and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

Descriptive statistics form an indispensable part of reports. Suitable tables and/or graphical presentations should illustrate clearly the important features of the primary and secondary variables and of key prognostic and demographic variables. The results of the main analyses relating to the objectives of the trial should be the subject of particularly careful descriptive presentation. When reporting the results of significance tests, precise p-values (e.g.'p=0.034') should be reported rather than making exclusive reference to critical values.

Although the primary goal of the analysis of a clinical trial should be to answer the questions posed by its main objectives, new questions based on the observed data may well emerge during the unblinded analysis. Additional and perhaps complex statistical analysis may be the consequence. This additional work should be strictly distinguished in the report from work which was planned in the protocol.

The play of chance may lead to unforeseen imbalances between the treatment groups in terms of baseline measurements not pre-defined as covariates in the planned analysis but having some prognostic importance nevertheless. This is best dealt with by showing that an additional analysis which accounts for these imbalances reaches essentially the same conclusions as the planned analysis. If this is not the case, the effect of the imbalances on the conclusions should be discussed.

In general, sparing use should be made of unplanned analyses. Such analyses are often carried out when it is thought that the treatment effect may vary according to some other factor or factors. An attempt may then be made to identify subgroups of subjects for whom the effect is particularly beneficial. The potential dangers of over-interpretation of unplanned subgroup analyses are well known (see also Section 5.7), and should be carefully avoided. Although similar problems of interpretation arise if a treatment appears to have no benefit, or an adverse effect, in a subgroup of subjects, such possibilities should be properly assessed and should therefore be reported.

Finally statistical judgement should be brought to bear on the analysis, interpretation and presentation of the results of a clinical trial. To this end the trial statistician should be a member of the team responsible for the clinical study report, and should approve the clinical report.

7.2 Summarising the Clinical Database

An overall summary and synthesis of the evidence on safety and efficacy from all the reported clinical trials is required for a marketing application (Expert report in EU, integrated summary reports in USA, Gaiyo in Japan). This may be accompanied, when appropriate, by a statistical combination of results.

Within the summary a number of areas of specific statistical interest arise: describing the demography and clinical features of the population treated during the course of the clinical trial programme; addressing the key questions of efficacy by considering the results of the relevant (usually controlled) trials and highlighting the degree to which they reinforce or contradict each other; summarising the safety

information available from the combined database of all the trials whose results contribute to the marketing application and identifying potential safety issues. During the design of a clinical programme careful attention should be paid to the uniform definition and collection of measurements which will facilitate subsequent interpretation of the series of trials, particularly if they are likely to be combined across trials. A common dictionary for recording the details of medication, medical history and adverse events should be selected and used. A common definition of the primary and secondary variables is nearly always worthwhile, and essential for meta-analysis. The manner of measuring key efficacy variables, the timing of assessments relative to randomisation/entry, the handling of protocol violators and deviators and perhaps the definition of prognostic factors, should all be kept compatible unless there are valid reasons not to do so.

Any statistical procedures used to combine data across trials should be described in detail. Attention should be paid to the possibility of bias associated with the selection of trials, to the homogeneity of their results, and to the proper modelling of the various sources of variation. The sensitivity of conclusions to the assumptions and selections made should be explored.

7.2.1 Efficacy Data

Individual clinical trials should always be large enough to satisfy their objectives. Additional valuable information may also be gained by summarising a series of clinical trials which address essentially identical key efficacy questions. The main results of such a set of trials should be presented in an identical form to permit comparison, usually in tables or graphs which focus on estimates plus confidence limits. The use of meta-analytic techniques to combine these estimates is often a useful addition, because it allows a more precise overall estimate of the size of the treatment effects to be generated, and provides a complete and concise summary of the results of the trials. Under exceptional circumstances a meta analytic approach may also be the most appropriate way, or the only way, of providing sufficient overall evidence of efficacy via an overall hypothesis test. When used for this purpose the meta-analysis should have its own prospectively written protocol.

7.2.2 Safety Data

In summarising safety data it is important to examine the safety database thoroughly for any indications of potential toxicity, and to follow up any indications by looking for an associated supportive pattern of observations. The combination of the safety data from all human exposure to the drug provides an important source of information, because its larger sample size provides the best chance of detecting the rarer adverse events and, perhaps, of estimating their approximate incidence. However, incidence data from this database are difficult to evaluate because of the lack of a comparator group, and data from comparative trials are especially valuable in overcoming this difficulty. The results from trials which use a common comparator (placebo or specific active comparator) should be combined and presented separately for each comparator providing sufficient data.

All indications of potential toxicity arising from exploration of the data should be reported. The evaluation of the reality of these potential adverse effects should take account of the issue of multiplicity arising from the numerous comparisons made. The evaluation should also make appropriate use of survival analysis methods to exploit the potential relationship of the incidence of adverse events to duration of exposure and/or follow-up. The risks associated with identified adverse effects should be appropriately quantified to allow a proper assessment of the risk/benefit relationship.

GLOSSARY

Bayesian Approaches

Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g. treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference.

Bias (Statistical & Operational)

The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as 'operational' bias. The other sources of bias listed above are referred to as 'statistical'.

Blind Review

The checking and assessment of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind, for the purpose of finalising the planned analysis.

Content Validity

The extent to which a variable (e.g. a rating scale) measures what it is supposed to measure.

Double-Dummy

A technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical. Supplies are prepared for Treatment A (active and indistinguishable placebo) and for Treatment B (active and indistinguishable placebo). Subjects then take two sets of treatment; either A (active) and B (placebo), or A (placebo) and B (active).

Dropout

A subject in a clinical trial who for any reason fails to continue in the trial until the last visit required of him/her by the study protocol.

Equivalence Trial

A trial with the primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

Frequentist Methods

Statistical methods, such as significance tests and confidence intervals, which can be interpreted in terms of the frequency of certain outcomes occurring in hypothetical repeated realisations of the same experimental situation.

Full Analysis Set

The set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle. It is derived from the set of all randomised subjects by minimal and justified elimination of subjects.

Generalisability, Generalisation

The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings.

Global Assessment Variable

A single variable, usually a scale of ordered categorical ratings, which integrates objective variables and the investigator's overall impression about the state or change in state of a subject.

Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Intention-To-Treat Principle

The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

Interaction (Qualitative & Quantitative)

The situation in which a treatment contrast (e.g. difference between investigational product and control) is dependent on another factor (e.g. centre). A quantitative interaction refers to the case where the magnitude of the contrast differs at the different levels of the factor, whereas for a qualitative interaction the direction of the contrast differs for at least one level of the factor.

Inter-Rater Reliability

The property of yielding equivalent results when used by different raters on different occasions.

Intra-Rater Reliability

The property of yielding equivalent results when used by the same rater on different occasions.

Interim Analysis

Any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to the formal completion of a trial.

Meta-Analysis

The formal evaluation of the quantitative evidence from two or more trials bearing on the same question. This most commonly involves the statistical combination of summary statistics from the various trials, but the term is sometimes also used to refer to the combination of the raw data.

Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Non-Inferiority Trial

A trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control).

Preferred and Included Terms

In a hierarchical medical dictionary, for example MedDRA, the included term is the lowest level of dictionary term to which the investigator description is coded. The preferred term is the level of grouping of included terms typically used in reporting frequency of occurrence. For example, the investigator text "Pain in the left arm" might be coded to the included term "Joint pain", which is reported at the preferred term level as "Arthralgia".

Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample)

The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations.

Safety & Tolerability

The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and haematology), vital signs, clinical adverse events (diseases, signs and symptoms), and other special safety tests (e.g. ECGs, ophthalmology). The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject.

Statistical Analysis Plan

A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Superiority Trial

A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo control).

Surrogate Variable

A variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible or practical.

Treatment Effect

An effect attributed to a treatment in a clinical trial. In most clinical trials the treatment effect of interest is a comparison (or contrast) of two or more treatments.

Treatment Emergent

An event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

Trial Statistician

A statistician who has a combination of education/training and experience sufficient to implement the principles in this guidance and who is responsible for the statistical aspects of the trial.

Protecting Human Research Participants

NIH Office of Extramural Research

PHRP Website

Protecting Human Research Participants

http://phrp.nihtraining.com/

Developed: 3/1/2008

Updated: 2/4/2011

Overview

The following information describes how to use this PDF to complete the online version of this course and receive a certificate of completion.

Internet Access Requirements

The PDF version of the NIH Office of Extramural Research **Protecting Human Research Participants** (*http://phrp.nihtraining.com*) is intended to allow registrants to review most course content in hard copy or off-line (without internet access). It is important to note that:

- You must have internet access to complete the quizzes and receive your certificate of completion.
- You need to have internet access if you wish to view the hyperlinked documents referenced throughout the PDF.

Tracking Your Completion and Testing Your Knowledge

Your progress through this course is tracked electronically and is recorded when you COMPLETE a section. Because you are not reading the materials on the website, once you finish reading a PDF section you should return to the online tutorial in order to "complete" each section. You may quickly click through each screen of the course section. This will allow the tutorial's electronic tracking to record your progress. If you must leave the online course prior to completion, it is advised that you first complete the section in which you are working. Completion of a section is registered when a checkmark appears to the left of the section title on the Main Menu screen.

Additionally, there are four quizzes that must be taken online. They are found at the end of the following course sections:

- Codes and Regulations,
- Respect for Persons,
- Beneficence, and
- Justice.

After submitting a quiz, it is scored. Once you have completed the quiz with a satisfactory score, a green check mark will appear to the right of the quiz score on the Main Menu screen. If you answer

less than the required number of questions correctly, the section must be reviewed and the quiz retaken until a satisfactory score has been attained. You may retake the quiz only after clicking through each screen of the online section.

Remember: your progress is only recorded when, on the Main Menu screen, you see a check mark:

1. To the left of each of the 7 sections AND
2. To the right of each of the 4 quizzes

If you do not see check marks after completing a section or a quiz, please **submit a ticket** through the online **Technical Support Form** (*http://esupport.nihtraining.com/index.php*).

Exiting and Re–entering the Online Program

You can exit and re-enter the program at any time. Log in with the same email address and password, and the program will remember which sections you have completed. Because the course is being tracked, book marking and returning to a screen will not work for purposes of tracking your completion. You MUST go through the log in process in order for your progress to be tracked.

Certificate of Completion

Once you have successfully completed the course, including the quizzes, a link will appear in the Main Menu allowing access to your certificate of completion.

To access your certificate, log in to the course and select the “Get Certificate” link from the Main Menu. If you do not remember your password, use the “Forgot your password” link on the Registration/Login screen.

This certificate may be accessed and printed at any time.

Resources

- **Primary source documents:** Within each section are links to primary source documents. These links are blue and italicized. When connected to the internet and clicked on, a new window will open with the source document content. *Please note that the security settings on your computer may generate a warning message asking you to confirm if the link you are trying to connect to is a trusted site. All links within this document have been verified.*
- **Glossary Terms**: Within each section terms found in the glossary are identified with red, italicized text. The glossary should be referenced for each of these terms, as the term definitions are pertinent to fully understand the topics.
- **Glossary:** There is a glossary section located at the end of this document.
- **Citations**: Citations are indicated within the text by a number appearing as a superscript next to the content. The corresponding citation information can be found within the left margin of the corresponding page in this document.
- **Case Studies**: Throughout the course, Case Studies are presented to illustrate the topics being discussed. Each case study will pose a hypothetical question with the answer provided on the following page. To receive the maximum benefit from the case study exercise, attempt to answer the question based on your knowledge of the topic before viewing the next page.

Questions

For questions related to the online course, please consult the “FAQ Page” which is accessible online from the Main Menu screen of the course.

Introduction

Research with human subjects can occasionally result in a dilemma for *investigators*. When the goals of the research are designed to make major contributions to a field, such as improving the understanding of a disease process or determining the efficacy of an intervention, investigators may perceive the outcomes of their studies to be more important than providing protections for individual participants in the research.

Although it is understandable to focus on goals, our society values the rights and welfare of individuals. **It is not considered ethical behavior to use individuals solely as means to an end**.

The importance of demonstrating respect for research participants is reflected in the principles used to define ethical research and the regulations, policies, and guidance that describe the implementation of those principles.

Who?

This course is intended for use by individuals involved in the design and/or conduct of National Institutes of Health (NIH) (*http://www.nih.gov/*) – funded human subjects research.

What?

This course is designed to prepare *investigators* involved in the design and/or conduct of research involving human subjects to understand their obligations to protect the rights and welfare of subjects in research. The course material presents basic concepts, principles, and issues related to the protection of research participants.

Why?

As a part of NIH's commitment to the protection of human subjects and its response to Federal mandates for increased emphasis on protection for human subjects in research, the NIH Office of Extramural Research released a policy on Required Education in the Protection of Human Research Participants (*http://grants.nih.gov/grants/guide/notice-files/not-od-00-039.html*) in June 2000. This course is specifically designed for

extramural investigators and is one (of many) possibilities for meeting the policy requirement.

Because this course is intended to allow *investigators* to fulfill the Required Education in the Protection of Human Research Subjects, it assumes that the investigators' research will be funded by NIH and is therefore subject to all U.S. Department of Health and Human Services (HHS) (*http://www.hhs.gov/*) regulatory and NIH policy requirements.

The information presented is neither prescriptive nor exhaustive and does not replace or supersede local, state, or Federal regulations applicable to human research or any institutional policies regarding the protection of human subjects.

Course Objectives

Upon completion of this course, you should be able to:

- Describe the history and importance of human subjects protections
- Identify research activities that involve human subjects
- Discover the risks a research project might pose to participants
- Understand how to minimize the risks posed by a research project
- Describe additional protections needed for vulnerable populations
- Understand additional issues that should be considered for international research
- Describe appropriate procedures for recruiting research participants and obtaining *informed consent*
- Identify the different committees that monitor human subjects protections
- Understand the importance of study design in the protection of research participants

The first module examines significant historical events that have contributed to the way we view the protections for participants in clinical research today.

History

What This Module Covers:

Before discussing the current system for the protection of human subjects in research, it is important to review some of the significant historical events that have influenced current ethical guidelines and HHS regulations.

This module covers the following topics:

- Goals and Principles of Human Subjects Protection
- Nazi Medical War Crimes
- Syphilis Study at Tuskegee
- Timeline of Important Historical Events

Goals and Principles of Human Subjects Protection

Human subjects are essential to the conduct of research intended to improve human health. As such, the relationship between *investigators* and human subjects is critical and should be based on **honesty, trust,** and **respect**.

Historical Events

Nazi Medical War Crimes (1939–1945)

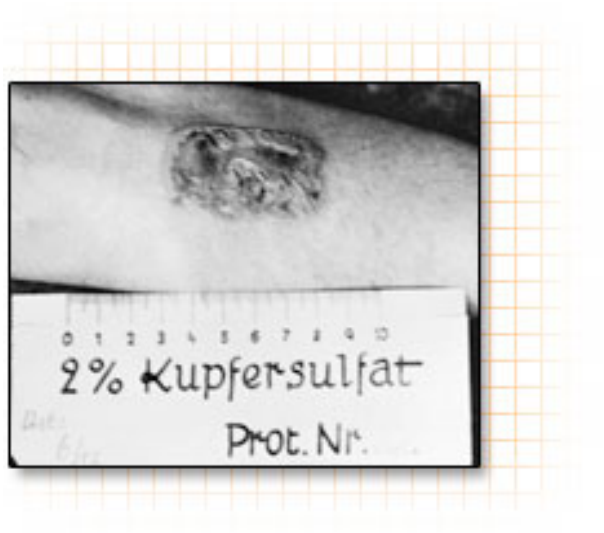

Photo source: Photo Archive, United States Holocaust Memorial Museum, courtesy of National Archives and Records Administration, College Park; used with permission.

This photograph documented the results of a medical experiment that included skin burns caused by doctors at the Ravensbrueck concentration camp in 1943. It was entered into evidence at the Doctors Trial at Nuremberg.

Although not the first example of harmful research on unwilling human subjects, the experiments conducted by Nazi physicians during World War II were unprecedented in their scope and the degree of harm and suffering to which human beings were subjected.

"Medical experiments" were performed on thousands of concentration camp prisoners and included deadly studies and tortures such as injecting people with gasoline and live viruses, immersing people in ice water, and forcing people to ingest poisons.

In December 1946, the War Crimes Tribunal at Nuremberg indicted 20 physicians and 3 administrators for their willing participation in the systematic torture, mutilation, and killing of prisoners in experiments. The Nuremberg Military Tribunals found that the defendants had:

- Corrupted the ethics of the medical and scientific professions
- Repeatedly and deliberately violated the rights of the subjects

The actions of these defendants were condemned as crimes against humanity. Sixteen of the twenty-three physicians/administrators were found guilty and imprisoned, and seven were sentenced to death.

The Nuremburg Code

Photo source: Photo Archive, United States Holocaust Memorial Museum, courtesy of Hedwig Wachenheimer Epstein; used with permission.

View from above of the defendants dock during a session of the Medical Case (Doctors) Trial in Nuremberg, which ran from December 9, 1946 to July 19, 1947.

In the August 1947 verdict, the judges included a section called **Permissible Medical Experiments**. This section became known as the Nuremberg Code (*http://ohsr.od.nih.gov/guidelines/nuremberg.html*) and was the first international code of research ethics.

This set of directives established the basic principles that must be observed in order to satisfy moral, ethical, and legal concepts in the conduct of human subject research. The Code has been the model for many professional and governmental codes since the 1950s and has, in effect, served as the first international standard for the conduct of research.

The Code provides ten Directives for Human Experimentation

1. Voluntary consent of the human subject is absolutely essential
2. The experiment must yield generalizable knowledge that could not be obtained in any other way and is not random and unnecessary in nature
3. Animal experimentation should precede human experimentation
4. All unnecessary physical and mental suffering and injury should be avoided
5. No experiment should be conducted if there is reason to believe that death or disabling injury will occur
6. The degree of risk to subjects should never exceed the humanitarian importance of the problem
7. Risks to the subjects should be minimized through proper preparations
8. Experiments should only be conducted by scientifically qualified investigators
9. Subjects should always be at liberty to withdraw from experiments
10. Investigators must be ready to end the experiment at any stage if there is cause to believe that continuing the experiment is likely to result in injury, disability or death to the subject

The Syphilis Study at Tuskegee

Photo source: Records of the Centers for Disease Control and Prevention.

An unidentified subject of the Tuskegee Syphilis Study provides a blood sample to study investigators in the early 1950s.

Arguably the most notorious example in the United States of the violation of the rights and welfare of human subjects was the long-term study of black males conducted by the United States Public Health Service in Tuskegee, Alabama. This study of the

natural history of untreated syphilis was initiated in the 1930s and continued until 1972.

The Syphilis Study at Tuskegee involved approximately 600 African-American men: about 400 with syphilis (cases) and about 200 without syphilis (controls). These men were recruited without *informed consent* and, in fact, were led to believe that some of the procedures done in the interest of research (e.g., spinal taps) were actually "special free treatment."

By 1936, it was apparent that many more infected men than controls had developed complications, and 10 years later, reports indicated that the death rate among those with syphilis was about twice as high as it was among the controls. In the 1940s, penicillin was found to be effective in the treatment of syphilis. The Syphilis Study at Tuskegee continued, however, and the men were neither informed about nor treated with the antibiotic.

Outcomes of the Syphilis Study at Tuskegee

The first accounts of this study appeared in the national press in 1972. The resulting public outrage led to the appointment of an ad hoc advisory panel by the Department of Health, Education and Welfare (which later was split into the Department of Education and the Department of Health and Human Services (HHS)) to review the study and develop recommendations to ensure that such experiments would never again be conducted.

Outcomes included:

1. National Research Act of 1974
2. Basic HHS Policy for Protection of Human Research Subjects (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html*)
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Timeline of Events in the History of Human Research Participants Protections

1932-1972 Syphilis Study at Tuskegee

More information may be found in:

- Brandt, AM. 1978. Racism and Research: The Case of the Tuskegee Syphilis Study. Hastings Center Report 8(6): 21-29 , and in
- Jones, JH. 1993. Bad Blood: Tuskegee Syphilis Experiment. Rev. ed. New York: Free Press.

1939-1945 Nazi Medical War Crimes

More information may be found in: Annas, GJ, and Grodin, MA. 1992. The Nazi Doctors and the Nuremburg Code, Human Rights in Human Experimentation. New York: Oxford University Press.

1944-1974 Cold War Human Radiation Experiments

The U.S. Government conducted more than 400 experiments to determine the effects of exposure to ionizing radiation on human health or to calibrate instruments designed to detect radiation. Most studies involved minimal risks and most of those involving greater than minimal risks included appropriate informed consent.

There were, however, cases where human subjects suffered physical injuries as a result of participating in studies that offered no prospect of direct benefit, or from interventions that were considered controversial at the time that were presented as standard practice.

See *http://www.hss.energy.gov/healthsafety/ohre/* for more information.

1946 Nuremberg Doctors' Trial

The individuals who conducted Nazi experiments during WWII were tried separately from other war criminals because of their professional status as physicians and the

horrendous and unique nature of their crimes. They were found guilty of “crimes against humanity.”

1947 Nuremberg Code

During the trial at Nuremberg, the judges codified fundamental ethical principles for the conduct of research. The Nuremberg Code set forth ten conditions to be met before research could be deemed ethically permissible. The Nuremberg Code became the first international standard for the conduct of research and introduced the modern era of protection for human research subjects.

See *http://www.hhs.gov/ohrp/archive/nurcode.html* for more information.

1947 American Psychological Association

The American Psychological Association began to develop a code of Ethical Standards that included issues in human subjects research.

See *http://www.apa.org/ethics/index.aspx* for more information.

1948 United Nations adopted Universal Declaration of Human Rights

The United Nations adopted The Universal Declaration of Human Rights, which was inspired by atrocities committed during World War II and states the conviction that human rights needed to be preserved at the international level.

See *http://www.un.org/Overview/rights.html* for more information.

1953 First U.S. Federal Policy for Protection of Human Subjects

The first U.S. Federal policy for the protection of human subjects was put into place for research conducted at the Clinical Center, NIH. This policy provided a mechanism for prospective review of proposed research by individuals having no direct

involvement or intellectual investment in the research. This system is the model for the current IRB system.

1963 Jewish Chronic Disease Hospital Study

Studies were undertaken at the Jewish Chronic Disease Hospital in New York to develop information about the human immune system's response to cancer. Live cancer cells were injected into chronically ill and debilitated patients who were told they were receiving a skin test. The investigators were eventually prosecuted and found guilty of fraud, deceit, and unprofessional conduct.

1963-1966 Willowbrook Study

Studies were carried out at the Willowbrook State School for "mentally defective persons," to gain an understanding of the transmission of infectious hepatitis and, subsequently, to test the effects of gamma globulin in preventing or ameliorating the disease.

Residents of Willowbrook, all of whom were children, were deliberately infected with hepatitis, by ingesting the stools of infected persons or receiving injections of more-purified virus preparations. The investigators maintained that hepatitis infection was inevitable for this population; however, critics asserted that the consent process was unethical because coercive tactics were employed as only children whose parents gave permission to participate in the studies were admitted to Willowbrook.

1964 Declaration of Helsinki

The World Medical Association drafted the first international agreement recommending ethical standards for clinical research.

The most recent version of the Declaration of Helsinki, in addition to translations of the Declaration into languages other than English, can be found on the WMA Web site (*http://www.wma.net/en/30publications/10policies/b3/index.html*).

Like the Nuremberg Code, the Declaration makes informed consent a central requirement for ethical research. The Declaration does, however, allow for surrogate consent when the research subject is incompetent, physically or mentally incapable of giving consent, or a minor. The Declaration, which has undergone multiple revisions, also states that research with these groups should be conducted only when the research is necessary to promote the health of the population represented and when this research cannot be performed on legally competent persons.

1966 Henry Beecher's Publication

Henry Beecher published an article in the New England Journal of Medicine describing 22 cases of human subjects research that involved ethical violations. Beecher argued against increasing regulations and in favor of responsible investigators. His perspective has been cited as influencing Federal policy to outline general requirements for informed consent and to delegate specific standards to local review processes. (Beecher, HK 1966. Ethics and Clinical Research. The New England Journal of Medicine 274(24):1354-1360.)

1974 Federal Protections for Human Subjects

After the Syphilis Study at Tuskegee was exposed, the Senate Committee on Labor and Human Resources held hearings on this study and other alleged health care abuses. The outcomes of these hearings were:

- The enactment of the National Research Act of 1974 requiring the Department of Health, Education, and Welfare to codify its policy for the protection of human subjects into regulations; and
- The formation of the National Commission for the Protections of Human Subjects of Biomedical and Behavioral Research, which drafted the Belmont Report.

1979 The Belmont Report

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This is the cornerstone document of ethical principles and HHS regulations for the protection of research subjects based on respect for persons, beneficence, and justice.

See *http://ohsr.od.nih.gov/guidelines/belmont.html* for more information.

1980 Publication of the FDA Regulations

FDA established regulations for clinical research: Code of Federal Regulations, Title 21, Part 50 (*http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr50_99.html*).

The FDA regulates research involving products regulated by the FDA, including research and marketing permits for drugs, biological products, and medical devices for human use, etc., whether or not HHS funds are used. If HHS funds are used in FDA-regulated research, the research must be compliant with both HHS and FDA regulations. More information about the FDA regulations and FDA-specific requirements can be found at *http://www.fda.gov/*.

1981 HHS & FDA Revise Regulations

In 1981, with the Belmont Report as foundational background, HHS and the Food and Drug Administration revised, and made as compatible as possible under their respective statutory authorities, their existing human subjects regulations.

1982 CIOMS Guidelines

The Council for the International Organization of Medical Sciences (CIOMS) published the International Ethics Guidelines for Biomedical Research Involving Human Subjects (CIOMS Guidelines). These guidelines are designed to assist investigators from technologically advanced countries to conduct ethical research involving human subjects in resource-poor countries. These 15 guidelines addressed issues including informed consent, standards for external review, recruitment of subjects, and more.

For further information about CIOMS and the Guidelines, refer to *http://www.cioms.ch/*.

1991 Publication of the Common Rule

The Federal Policy for the Protection of Human Subjects or the "Common Rule" was published in 1991 and codified in separate regulations by 15 Federal departments and agencies

See: *http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html* for more information.

1993-1994 Revelation of Human Radiation Experiments

President Clinton established the Advisory Committee on Human Radiation Experiments to investigate human radiation experiments during the period 1944 to 1974; examine cases in which radiation was intentionally released into the environment for research purposes; identify ethical and scientific standards for evaluating these events; and deliver recommendations to the Human Radiation Interagency Working Group. The Committee recommended government apologies and financial compensation in cases where:

- Efforts were made by the government to keep information secret from these individuals, their families or the public to avoid embarrassment or potential legal liability, and where this secrecy had the effect of denying individuals the opportunity to pursue potential grievances
- There was no prospect of direct medical benefit to the subjects, or interventions considered controversial at the time were presented as standard practice, and physical injury attributable to the experiment resulted

See *http://www.hss.energy.gov/healthsafety/ohre/roadmap/achre/index.html* for more information.

1995 Establishment of The National Bioethics Advisory Commission

The National Bioethics Advisory Commission (NBAC) was established to promote the protection of the rights and welfare of human subjects in research, identify bioethical issues arising from research on human biology and behavior, and make recommendations to governmental entities regarding their application. The NBAC term ended in 2001.

See *http://bioethics.georgetown.edu/nbac/* for more information.

1996 Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule

In response to a congressional mandate in the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the U.S. Department of Health and Human Services (HHS) issued the regulations Standards for Privacy of Individually Identifiable Health Information. For most covered entities, compliance with these regulations, known as the “Privacy Rule”, was required as of April 14, 2003.

The Privacy Rule was enacted in response to public concerns over potential abuses of the privacy of health information. Implementation and oversight of the Privacy Rule are the responsibility of the HHS Office for Civil Rights. Additional information about how the Privacy Rule impacts research can be found at *http://privacyruleandresearch.nih.gov* and *http://www.hhs.gov/ocr/privacy/*.

1999 The Death of Jesse Gelsinger

On September 17, 1999, 18 year-old Jesse Gelsinger became the first subject in a gene transfer clinical trial to die from a reaction to a recombinant viral vector. Jesse suffered from a deficiency of ornithine-transcarbamylase (OTC), a necessary enzyme, and enrolled in a Phase I dose-escalation trial at the University of Pennsylvania. The clinical trial involved the injection of an adenoviral vector containing the gene. Jesse died after receiving the injection.

Subsequent investigations found that the Principal Investigator was an inventor for the technology used in the trial and held equity in the start-up company to which the

technology was licensed. This case brought significant attention to the issue of financial conflicts of interest in research. Additional information about financial conflict of interest can be found on the NIH Conflict of Interest (COI) Page (*http://grants.nih.gov/grants/policy/coi/index.htm*). The HHS regulations governing conflicts of interest, "Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought", can be found at 42 CFR 50, Subpart F (*http://grants.nih.gov/grants/compliance/42_CFR_50_Subpart_F.htm*).

2000 The Office of Human Research Protections

The Office of Human Research Protections (OHRP) was elevated to the level of the U.S. Department of Health and Human Services, replacing the NIH Office for Protection from Research Risks (OPRR). The OHRP provides leadership for all 17 Federal agencies that carry out research involving humans under the Common Rule regulations. The Office has regulatory authority for the protection of human subjects in research and policies and procedures for Institutional Review Boards.

To learn more about OHRP, visit *http://www.hhs.gov/ohrp/*.

2004 The Secretary's Advisory Committee on Human Research Protections

The Secretary's Advisory Committee on Human Research Protections (SACHRP) was established to provide expert advice and recommendations to the Secretary of Health and Human Services and the Assistant Secretary for Health on issues and topics pertaining to or associated with the protection of human research subjects.

See *www.hhs.gov/ohrp/sachrp* for more information.

Codes and Regulations

What This Module Covers:

- The Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research (*http://ohsr.od.nih.gov/guidelines/belmont.html*)
- HHS Regulations for the Protection of Human Subjects, 45 CFR 46 (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html*)

The Objectives For This Module Are:

- To identify the three principles of ethical human subjects research identified in the Belmont Report
- To comprehend the current HHS regulations, including:
    - Risks associated with participation in research and appropriate protections against risks
    - Vulnerable populations that need specific protections
    - Situations in which research involving humans is exempt from regulatory requirements

The Belmont Report

Following the public outrage over the Syphilis Study at Tuskegee, Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974. The National Commission was charged with:

1. Identifying the ethical principles to guide all research involving human subjects
2. Developing guidelines for the conduct of ethical research involving human subjects

In 1979, the National Commission drafted The Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects of Research (*http://ohsr.od.nih.gov/guidelines/belmont.html*).

The Belmont Report identified **three principles** essential to the ethical conduct of research with humans:

1. **Respect for persons**
2. **Beneficence**
3. **Justice**

These three basic principles serve as the foundation of the current HHS regulations and guidelines for the ethical conduct of human subjects research supported by HHS.

Respect for Persons

> *"To respect autonomy is to give weight to the autonomous person's considered opinions and choices while refraining from obstructing his or her actions..."*
> *– Belmont Report*

The principle of respect for persons can be broken down into two basic ideas:

1. Individuals should be treated as autonomous agents.

   An *autonomous person* is able to:

   - Consider the potential harms and benefits of a situation
   - Analyze how those risks and potential benefits relate to his or her personal goals and values
   - Take action based on that analysis

   Prospective research participants must be given the information they need to determine whether or not they want to participate in research. There should be no pressure to participate and ample time to decide. Respect for persons demands that participants enter into the research voluntarily and with adequate information. This is called *informed consent*, and will be covered in detail in other sections of this training.

2. Persons with diminished autonomy are entitled to additional protections.

   Special provisions may need to be made when an individual's comprehension is severely limited or when a class of research participants is considered incapable of informed decision making (e.g. *children*, people with severe developmental disorders, or individuals suffering from dementias). Even for these persons, however, respect for persons requires giving them the opportunity to choose, to the extent they are able, whether or not they wish to participate in research activities. In some cases, respect for persons may require seeking the *permission* of other parties, such as a parent or legal guardian.

The challenges in applying the **Belmont principle of respect for persons** are in:

- Making sure that potential participants comprehend the risks and potential benefits of participating in research
- Avoiding influencing potential participants' decisions either through explicit or implied threats (*coercion*) or through excessive *compensation* (*undue influence*)

Beneficence

> *"Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term beneficence is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation."*
> *– Belmont Report*

Two general rules have been articulated as complementary expressions of beneficent actions:

1. Do no harm
2. Maximize possible benefits and minimize possible harms

The challenge inherent in applying the **Belmont principle of beneficence** is how to determine when potential benefits outweigh considerations of risks and vice versa.

Justice

> *"Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects."*
> *–Belmont Report*

Justice requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research.

The principle of justice may arise in decisions about inclusion and exclusion criteria for participation in research and requires *investigators* to question whether groups are considered for inclusion simply because of their availability, their compromised

position, or their vulnerability — rather than for reasons directly related to the problem being studied.

The challenge of applying the **Belmont principle of justice** is how to decide which criteria should be used to ensure that harms and benefits of research are equitably distributed to individuals and populations.

Review

The Belmont Report identifies three principles essential to the ethical conduct of research with humans: Respect for Persons, Beneficence, and Justice. In the table below, each statement is an example of the application of one of these three principles, specified on the right.

Investigators should allow individuals to make their own decisions.	**Respect for Persons**
Individuals who are less able to make decisions for themselves require additional protections.	**Respect for Persons**
Investigators should design research studies so as to maximize benefits and to minimize risks to individuals.	**Beneficence**
The burdens and benefits of research should be fairly distributed among individuals, groups, societies, etc.	**Justice**

The HHS Regulations – Protection of Human Subjects

The ethical principles for research involving human subjects described in the Belmont Report are codified in the Code of Federal Regulations, 45 CFR 46 (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html*). The NIH follows all Subparts of the HHS regulations:

Subpart A (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subparta*) – Basic HHS Policy for Protection of Human Research Subjects

Subpart B (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb*) – Additional Protections for *Pregnant* Women, Human *Fetuses* and *Neonates* Involved in Research

Subpart C (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc*) – Additional Protections Pertaining to Biomedical and Behavioral Research Involving *Prisoners* as Subjects

Subpart D (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd*) – Additional Protections for Children Involved as Subjects in Research

Subpart E (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subparte*) – Registration of Institutional Review Boards (effective July 14, 2009)

Subpart A - Basic HHS Policy for Protection of Human Research Subjects

Subpart A (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subparta*), also called **"The Common Rule"**, describes the required protections for all human subjects.

Subpart A defines a ***human subject*** as "a living individual about whom an *investigator*...conducting research obtains:

1. Data through intervention or interaction with the individual, or
2. Identifiable private information."

Subpart A defines ***research*** as "a systematic investigation...designed to develop or contribute to generalizable knowledge."

This definition includes:

- Research development
- Testing
- Evaluation

Case Study: Human Heart Study

An *investigator* will be using human hearts in order to study factors leading to heart failure. One group of normal, control hearts will be obtained from cadavers. A set of diseased hearts will be obtained from individuals who are to receive a heart transplant.

Does this study involve human subjects?

Case Study: Human Heart Study

Does this study involve human subjects?

The use of healthy hearts from cadavers does not constitute human subjects research, because the individuals from whom the hearts will be obtained are not living, but the use of the diseased hearts removed during transplant surgery is human subjects research, since the donors are alive.

This study does involve human subjects.

Additional Protections

The Belmont principle of respect for persons states, in part, that individuals with *diminished autonomy* may need additional protections. ***Subparts B, C, and D*** describe additional protections for some of the populations that are considered particularly vulnerable:

Subpart B (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb*) Additional Protections for *Pregnant* Women, Human *Fetuses* and *Neonates* Involved in Research

Subpart C (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc*) Additional Protections Pertaining to Biomedical and Behavioral Research Involving *Prisoners* as Subjects

Subpart D (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd*) Additional Protections for *Children* Involved as Subjects in Research

Vulnerable Populations

Subparts B, C and D define the specific categories of research in which *pregnant women*, human *fetuses* and *neonates*, *prisoners*, or *children* respectively may be involved. The subparts describe additional requirements for *informed consent*, and may specify additional responsibilities for the Institutional Review Board (IRB) when reviewing research involving these populations, and list the requirements for research that need additional levels of review and approval.

Other vulnerable populations include, but are not limited to, mentally disabled persons and economically and/or educationally disadvantaged persons. While the regulations do not specify what additional protections are necessary for these groups, the HHS regulations (45 CFR 46.111) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111*) do require that *investigators* include additional safeguards in the study to protect the rights and welfare of these individuals “when some or all of the subjects are likely to be vulnerable to *coercion* or *undue influence*.”

Case Study: Fetal Imaging

Read the study description below and determine if **Subparts B, C or D** of HHS Regulations require additional protections for the study's participants:

A study proposes to test a novel fetal imaging technology designed to enhance image quality and allow physicians to assess more accurately prenatal health. This technology has been tested both on pregnant mammals and non-pregnant women with no adverse effects. *Pregnant* women will be recruited at their regularly scheduled prenatal check-ups and those who consent to participate will receive the experimental scan.

Do Subparts B, C or D require that participants in this study receive additional protections?

Case Study: Fetal Imaging

Do Subparts B, C or D require that participants in this study receive additional protections?

Because the research will be conducted with pregnant women and fetuses, the requirements for additional protections contained in **Subpart B** apply.

Additional protections for participants in this study are required under Subparts B, C, or D.

Case Study: Observational Study of Challenges Returning to Work

Read the study description below and determine if **Subparts B, C or D** of HHS Regulations require additional protections for the study's participants:

A study proposes to observe the challenges for former *prisoners* returning to office jobs. Researchers will recruit individuals who have spent over ten years in prison, have completed their sentences, and are now interviewing for office jobs.

Do Subparts B, C or D require that participants in this study receive additional protections?

Case Study: Observational Study of Challenges Returning to Work

Do Subparts B, C or D require that participants in this study receive additional protections?

The participants in this research are not considered prisoners, per **Subpart C**, because they have completed their period of involuntary confinement and are no longer "confined or detained in a penal institution" (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc*) nor are they "detained pending arraignment, trial, or sentencing."

No additional protections for participants in this study are required under Subparts B, C or D.

Case Study: Treatment and Prevention Research in Adolescents

Read the study description below and determine if **Subparts B, C or D** of HHS Regulations require additional protections for the study's participants:

A study proposes to examine the effectiveness of a medical treatment and prevention program for adolescents in a location where the legal age for consent to such treatment is 12. The adolescents involved range from ages 12 to 17.

Do Subparts B, C or D require that participants in this study receive additional protections?

Case Study: Observational Study of Challenges Returning to Work

Do Subparts B, C or D require that participants in this study receive additional protections?

The regulatory definition of children depends both on the local laws and on the specific treatments or procedures that will be involved in the research. Because the location in which the research will be conducted allows 12-year-olds to consent to the treatment, the participants in this research are not considered children under the HHS regulations and can provide informed consent to participate in the study. While the regulations do not require the additional protections of **Subpart D** for children in this study, the IRB may require some additional protections if they feel that the adolescents who will be involved in the study are vulnerable.

No additional protections for participants in this study are required under Subparts B, C or D.

Requirements for Federal Support of Human Subjects Research

The HHS regulations (45 CFR 46.120 *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.120*) require that Federal Departments and Agencies that conduct or support human subjects research must evaluate all applications for research using the following criteria:

- Risks to the subjects
- Adequacy of protection against these risks
- Potential benefits of the research to the subjects and others
- Importance of the knowledge gained or to be gained

Equivalent Protections for International Research

When research covered by the HHS regulations takes place in countries other than the United States, the HHS regulations (45 CFR 46.101(h)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101*) allow a department or agency head to approve the substitution of alternative polices, codes, or regulations to protect human subjects in lieu of the requirements of 45 CFR 46 as long as the alternatives afford protections that are at least equivalent to those provided in 45 CFR 46.

In a Federal Register Notice (*http://edocket.access.gpo.gov/2006/E6-10511.htm*) on July 7, 2006, HHS clarified that the requirements of the HHS regulations (45 CFR 46) must be satisfied for all HHS-conducted or -supported research covered by the Federalwide Assurance (*http://www.hhs.gov/ohrp/assurances/assurances/index.html*), regardless of whether the research is conducted domestically or internationally. As of the publication of that Notice, HHS had not deemed any other procedural standards equivalent to 45 CFR 46.

Engagement in Human Subjects Research

Each institution that is engaged in NIH-funded human subjects research must:

- Obtain or hold a current Federalwide Assurance (FWA) (*http://www.hhs.gov/ohrp/assurances/assurances/index.html*), assuring that an institution will comply with HHS regulatory requirements for the protection of human subjects (this is obtained from the HHS Office for Human Subjects Protections (OHRP)); and
- Certify to NIH that grant applications and contract proposals describing research involving human subjects has been reviewed and approved by an Institutional Review Board (IRB) designated in the FWA, and will be subject to continuing review by an IRB.

IRBs are committees that consist of 5 or more members with varying expertise and diversity that are responsible for reviewing and approving human subjects research activities on behalf of institutions.

The Common Rule specifies:

- IRB membership (45 CFR 46.107) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107*)
- IRB functions & operations (45 CFR 46.108) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.108*)
- IRB review of research (45 CFR 46.109 and 45 CFR 46.110) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.109*) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.110*)
- Criteria for IRB approval of research (45 CFR 46.111) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111*)

And more!

The roles and responsibilities of IRBs are discussed extensively in the module on **Beneficence**.

Exemptions

The HHS regulations describe categories of human subjects research that may be exempt from requirements described in the HHS regulations including IRB oversight.

Studies proposing only research that falls under one or more of the exempt categories of research do not require IRB review and approval, but the HHS Office for Human Research Protections (OHRP) has stated that: "Institutions should have a clear policy in place on who shall determine what research is exempt under 46.101(b)" (*http://www.hhs.gov/ohrp/policy/hsdc95-02.html*) and that *investigators* should not be able to determine whether or not their own research is exempt. This authority should rest with the IRB or other entity designated by the institution.

The exemptions can be found at 45 CFR 46.101(b) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101*).

Codes and Regulations: Summary

This module examined:

- The three basic ethical principles described in the Belmont Report
- The subsequent codification of these principles in 45 CFR 46 of the Code of Federal Regulations

The Belmont Report summarizes the three basic ethical principles of clinical research as:

1. Respect for persons
    - Individuals should be treated as *autonomous agents*
    - Persons with *diminished autonomy* are entitled to additional protections
2. Beneficence
    - Do no harm
    - Maximize possible benefits and minimize possible harms
3. Justice
    - Requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research

45 CFR 46 codifies these basic principles:

- **Subpart A** describes the required protections for all Federally conducted or supported human subjects research
- **Subpart B** covers additional protections for pregnant women, human *fetuses* and *neonates*
- **Subpart C** outlines additional protections pertaining to biomedical and behavioral research involving *prisoners* as subjects
- **Subpart D** provides for additional protections for *children*

Additionally, the regulations discuss methods of determining whether research is exempt from the regulations.

Codes and Regulations: Quiz

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Respect for Persons

What This Module Covers:

- The *informed consent* process
- Requirements for documentation of informed consent
- Waivers of informed consent
- *Diminished autonomy* and *legally authorized representatives*
- Participation of *pregnant women* in research
- *Assent* from *children* and *permission* from parents
- Obtaining informed consent from *prisoners*
- Community consent

The Objectives For This Module Are:

- To outline the requirements for informed consent
- To state when waivers of informed consent and legally authorized representatives are appropriate

Respect for Persons

> *"To respect autonomy is to give weight to the autonomous persons considered opinions and choices while refraining from obstructing his or her actions…"*
> *—Belmont Report*

The principle of respect for persons can be broken down into two basic ideas:

1. Individuals should be treated as *autonomous agents*
2. Persons with *diminished autonomy* are entitled to additional protections

Informed Consent

The Belmont principle of respect for persons is primarily applied by requiring that all human subjects research participants provide voluntary informed consent to participate in research.

The three fundamental aspects of informed consent are:

Voluntariness

Individuals' decisions about participation in research should not be influenced by anyone involved in conducting the research: "...consent must be freely given or truly voluntary." [1]

1. Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.189.

Comprehension

Individuals must have the mental or decisional capacity to understand the information presented to them in order to make an informed decision about participation in research.

Disclosure

HHS regulations (45 CFR 46.116(a)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*) require that researchers disclose:

1. The purpose of the study
2. Any reasonably foreseeable risks to the individual
3. Potential benefits to the individual or others
4. Alternatives to the research protocol
5. The extent of confidentiality protections for the individual
6. *Compensation* in case of injury due to the protocol
7. Contact information for questions regarding the study, participants' rights, and in case of injury
8. The conditions of participation, including right to refuse or withdraw without penalty

This disclosure must be made in such a way that it provides a **reasonable person** the information she or he would need in order to make an informed decision.

The HHS regulations (45 CFR 46.116) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*) require that *investigators* obtain legally effective *informed consent* from prospective participants in a way that allows them to consider whether or not to participate and that minimizes the possibility for *coercion* or *undue influence*.

Potential participants must understand that enrolling in the research is voluntary and that they may withdraw from the study at any time without penalty or loss of benefits (45 CFR 46.116(a)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*).

In order for participation in research to be voluntary, the potential for coercion and undue influence must be minimized.

Case Study: Sleeping Sickness Study on Campus

An *investigator*, who is a professor at a large university, is developing a grant application for submission to the NIH to study sleeping sickness (trypanosomiasis). This study will investigate surface antigen expression in trypanosomes, the parasite that causes sleeping sickness, in order to develop a vaccine. These parasites grow in human blood and lymph.

The study will require fresh human blood daily for several months, and thus will require research participants. A research assistant will maintain a schedule of research participants to ensure that the study performs one collection per day and that blood collections are in accordance with American Red Cross Blood Donation Eligibility Guidelines (*http://www.redcrossblood.org/donating-blood/eligibility-requirements*), i.e., healthy, weigh at least 110 pounds, and have not donated a pint (570 ml.) of whole blood in the last 8 weeks (56 days). Participants will be compensated.

It is now time to make a decision about **recruitment** of the research participants.

Based on the number of students and employees in her classes and lab, the researcher feels confident that she will have enough participants needed for the proposed research if she simply recruits among them. But she knows that some colleagues advertise their studies through postings on campus. The *investigator* is faced with two possible options for recruiting normal, healthy research participants:

- Recruit the students in her upper level classes and the technicians from her lab, and give $5 *compensation* to participants per blood draw, or
- Recruit from the general university population (students, faculty and staff) by posting fliers around campus, and give $5 compensation to participants per blood draw

The investigator discusses the grant application and proposed research procedures with you. You think that the compensation plan is appropriate and that $5 would not be an *undue influence* for either population to participate.

From which population would you advise the researcher to recruit?

A. *Recruit the students in her upper level classes and the technicians from her lab to participate in the study.*

B. *Post fliers around campus to recruit participants from the campus population (students, faculty, and staff).*

Case Study: Sleeping Sickness Study on Campus

From which population would you advise the researcher to recruit?

A. *Recruit the students in her upper level classes and the technicians from her lab to participate in the study.*

B. *Post fliers around campus to recruit participants from the campus population (students, faculty, and staff).*

Asking for study participants from a population over which a researcher has authority is not the best idea. It is generally agreed that students and employees are groups that can be vulnerable to coercion. Even though the researcher may feel confident that she would never let her students' and employees' decisions about participation affect her opinions about them, her students and employees might feel pressured to participate simply because she is in a position of authority.

Recruiting for the study participants from the students, faculty and staff of the university is the best choice. However, in this situation, the recruitment plans include the entire campus community. As long as she does not mention her proposed research in her classes and there is no indication that she will be in a position of authority over the individuals who choose to contact her, the proposed population is not vulnerable to coercion.

The researcher should post fliers around campus to recruit participants from the campus population (students, faculty, and staff) - Answer B is correct.

Informed Consent

Informed consent should be understood as an **on-going process** rather than a level of legal protection for an institution. It is not intended to be a one-time act of having a participant sign a form.

Informed consent is designed to inform research subjects about the purpose, risks, potential benefits and alternatives to the research that allows people to make a decision about whether or not to participate based on their own goals and values. This exchange of such information should occur at enrollment and throughout the study.

Investigators are responsible for providing information during the *informed consent* process in a manner that is understandable to the potential participants. *Investigators* should not enroll anyone in a study unless the investigator is confident that the individual comprehends all information disclosed and agrees to procedures described during the informed consent process.

Investigators can use methods in addition to a **consent form** to enhance individuals' comprehension. Some examples include:

- Oral presentations that provide potential participants with the opportunity to discuss the information and ask questions
- Providing additional educational materials, such as brochures, about research in general and/or the specific procedures that will be used in the study
- Video presentations that familiarize potential participants with the procedures that will be used in the study

The informed consent process must be delivered in "… language that is understandable to the subject …" (45 CFR 46.116) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*). This may mean adjusting the reading levels of documents provided or translating documents and presentations into the language with which participants are most comfortable.

Case Study: Sleeping Sickness Study on Campus

Now that your colleague studying sleeping sickness has decided on the method of recruitment for the study participants, she must write an *informed consent* document for the participants to sign.

The researcher has prepared two different draft consent documents and must select one to submit to her IRB for review.

Read the two consent documents and then choose the document that best informs the potential participants about the study in which they will enroll:

Consent Document 1

Surface Antigen Expression in Trypanosomes

Dr. X

You are invited to participate in this study by giving blood on a voluntary basis, but no more than five times in an eight week period. The research project is anticipated to continue for four years.

All blood draws will be performed by qualified technicians at the Medical Center Blood Bank. 100 ml of blood will be withdrawn from a vein in your arm.

Although you will not benefit directly from participating in this study, you will make a major contribution to the information known about trypanosomiasis, also known as sleeping sickness. In the future, others may benefit because scientists and doctors will learn about how parasites cause sleeping sickness, and will develop vaccines to prevent it.

You will be paid $5 for the time and travel required to give blood.

Your signature on this form means that you understand that participation is voluntary, and you may withdraw from the study at any time.

_____

Signature of Participant

Contact information for Dr. X:
Email: drx@university.edu
phone: 123-456-7890

Consent Document 2

Surface Antigen Expression in Trypanosomes

Dr. X

Dr. X's laboratory studies the parasite which causes trypanosomiasis, also known as sleeping sickness. This study will look at the effects of different surface antigens (proteins) produced by the parasites in human blood. The goal is to identify how different surface antigens are expressed by the parasites.

You are invited to participate in this study by giving blood on a voluntary basis, but no more than five times in an eight week period. The research project is anticipated to continue for four years.

All blood draws will be performed by qualified technicians at the Medical Center Blood Bank. 100 ml of blood will be withdrawn from a vein in your arm. None of the procedures are experimental.

During the collection of blood, you may experience discomfort and bruising at the site of collection. To minimize these risks, you will be asked to lie down while an experienced technician collects the blood sample. You may feel light-headed after having blood drawn. If you feel faint, you should not get up and should notify a nurse.

Although you will not benefit directly from participating in this study, you will make a major contribution to the information known about sleeping sickness. In the future, others may benefit because scientists and doctors

will learn about how parasites cause sleeping sickness and will develop vaccines to prevent it.

A research assistant will keep a record of all blood draws in a secure database. Only the professional staff at the Medical Center will know the identity of study participants.

You will be paid $5 for the time and travel required to give blood. If you feel that you have been injured as a direct result of participating in the study, please contact Dr. X at 123-456-7890.

Your signature on this form means that you understand the information presented, and that you want to participate in the study. You understand that participation is voluntary, and you may withdraw from the study at any time.

_____

Signature of Participant

Contact information for Dr. X:
Email: drx@university.edu
phone: 123-456-7890

Which of these two consent documents would you choose to use?

Case Study: Sleeping Sickness Study on Campus

Which of these two consent documents would you choose to use: Consent Document 1 or 2?

Consent Document 1 does include information regarding potential benefits to others and *compensation* for participants, there is no information regarding the following:

1. Risks for the participant
2. Confidentiality protections
3. Contact information for questions regarding the study
4. The conditions of participation, including right to refuse or withdraw without penalty

Consent Document 2 includes the following required elements of informed consent:

1. The purpose of the study
2. Foreseeable risks/discomforts to the individual
3. Potential benefits to the individual or others
4. Confidentiality protections for the individual
5. Compensation plan
6. Contact information for questions regarding the study, participants' rights, and in case of injury
7. The conditions of participation, including right to refuse or withdraw without penalty

Therefore, **Consent Document 1** does not include all of the required elements of informed consent (45 CFR 46.116) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*) and does not protect against the perception of *coercion*. **Consent Document 2** contains all of the required elements of informed consent (45 CFR 46.116) and protects against the perception of coercion by emphasizing the fact that participation is voluntary and explaining how someone can withdraw from the study if they wish.

Consent Document 2 is the best choice.

Waivers of Informed Consent

The HHS regulations (45 CFR 46.116(c)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*) allow institutional review boards (IRBs) to waive or alter **some or all of the required elements of** *informed consent* if all of the following conditions are met:

1. "The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; (iv) possible changes in methods or levels of payments for benefits or services under those programs, and
2. The research could not practicably be carried out without the waiver or alteration."

The HHS regulations (45 CFR 46.116(d)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116*) also allow IRBs to waive or alter some or all of the required elements of *informed consent* if all of the following conditions are met:

1. "The research involves no more than *minimal risk* to the subjects
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation"

Practicability and Waivers of Informed Consent

Decisions about waivers of informed consent often concern the issue of **practicability**. Although practicability is not defined in the HHS regulations, it is not sufficient for an *investigator* to argue simply that seeking consent would be time-consuming or incur additional cost.

In some situations, a waiver of *informed consent* may be appropriate for a medical record review or for using existing data or specimens that can be linked to identifiable individuals. Specific decisions regarding practicability are made by the IRB.

Case Study: New Analyses of Existing Data

An *investigator* has collected identifiable data from participants in a research study. He has completed the analyses that were originally proposed and described in the NIH grant application, the protocol approved by the IRB, and the *informed consent* document approved by the IRB. The informed consent document made no mention of using the data in additional research but gives permission for the investigator to re-contact the participants.

Now, based on new hypotheses, the investigator plans to conduct new analyses to fulfill purposes different from those described in the informed consent document, the NIH grant application and the IRB-approved protocol. He knows that he needs to obtain approval for the new research from his IRB and his NIH Program Official.

Does the investigator need to obtain new informed consent from the participants?

Case Study: New Analyses of Existing Data

Does the investigator need to obtain new informed consent from the participants?

Either answer may be correct.

The investigator needs to obtain informed consent unless:

- The criteria for a waiver are met, and
- The IRB has approved a waiver of informed consent.

Requirements for Documentation of Informed Consent

The HHS regulations **require that** *informed consent* **be documented** using a written form that either contains all of the required elements (45 CFR 46.116(a)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*) or a short form that states that all of the required elements have been presented orally. This form must be signed by either the participant or the participant's *legally authorized representative* (45 CFR 46.117) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.117*).

The HHS regulations (45 CFR 46.117(c)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.117*) allow IRBs to waive the requirement for **documented** informed consent if they find that either:

1. "The only record linking the participant to the research would be the (informed) consent document and the principal risk to the participants would be the potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern, or
2. The research presents no more than *minimal risk* to the participants and involves no procedures for which written consent is normally required outside of the research context."

Diminished Autonomy

An individual's *autonomy* can be affected by several factors including age, cognitive impairment, illness, and treatments. An individual's capacity to consent to a particular study should be assessed based on:

1. The individual's level of capacity, and
2. The complexity and risks of the study, i.e., the capacity needed for an individual to be able to understand the study well enough to consent to participate

Decisional Capacity and Legally Authorized Representatives

The Belmont principle of respect for persons states that investigators need to make special provisions when including individuals in research who have diminished capacity for making decisions in their own best interests.

The HHS regulations, therefore, require that *legally authorized representatives* provide voluntary *informed consent* for individuals with diminished capacity to participate in research (45 CFR 46.116) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*).

While the HHS regulations allow for legally authorized representatives to make substituted decisions for individuals who need assistance, *investigators* should obtain consent from the participants to the extent possible. Because some individuals may be only temporarily or intermittently incapacitated (e.g., due to injury or medications), investigators should attempt to approach these individuals at a time when they do have the capacity to consent to research. If a participant regains the capacity to consent to research after the research has begun, investigators should obtain the participant's informed consent before continuing his or her participation in the study.

Participation of Pregnant Women in Research

Because research involving *pregnant women* may affect the woman, the *fetus*, or both the woman and the fetus, additional issues must be considered for studies of pregnant women.

The HHS regulations require:

- Preclinical studies be completed prior to the involvement of pregnant women
- A consideration of risks and potential benefits for the fetus and pregnant woman

The HHS regulations prohibit:

- Inducements of any kind to terminate a pregnancy
- *Investigators* from taking part in decisions about terminating a pregnancy
- Investigators from determining the viability of a *neonate*

Investigators, IRBs, and funding agencies must comply with requirements described in Subpart B of the HHS regulations.

Children's Participation in Research

Children may not have full capacity to make decisions in their own best interests; and therefore:

- Children are considered a vulnerable population, and
- Children are unable to provide "legally effective *informed consent*" as required by the HHS regulations at 45 CFR 46.116 *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*)

Because children cannot provide informed consent, children provide *assent* to participate in research, to the extent that they are able, and parents/guardians give *permission* for a child to participate in research.

The additional regulatory requirements of assent and permission for research involving children (45 CFR 46.408) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.408*) are intended to make sure that *investigators* respect the decisions of both children and their parents. Parental permission must be obtained for research involving children "in accordance with and to the extent that consent is required by 45 CFR 46.116."

Assent and Permission for Children's Participation in Research

The ages, maturity and psychological states of the *children* involved in the research should be taken into account when determining whether children have the capacity to *assent*. This determination is made by the IRB. The IRB may require that *investigators* conduct an individual assessment of each child's ability to assent or may make a general determination for all children involved in the study.

The content and language of the assent process should be appropriate to the age and education/developmental stage of the children providing assent. It may be necessary to have multiple assent documents or assent processes if the children to be enrolled in the research are of different ages or at different stages of development.

Case Study: Lack of Assent from a Child

A 7-year-old *child* has a rare genetic disorder. No treatment is currently available. You have designed a longitudinal study that will examine the progression of the disorder. The study will involve standard physical and psychological examinations, including drawing 10ml of blood 4 times per year.

After enrollment, at which time the parents provided *permission* for the child to participate in the study and the child provided assent, he panics and screams that he doesn't want to participate and wants to go home when he sees the nurse holding a needle for the blood draw. The parents are present and want the child to participate.

Do you need to withdraw this child from your study because he has withdrawn his assent?

Case Study: Lack of Assent from a Child

Do you need to withdraw this child from your study because he has withdrawn his assent?

A number of issues should be considered to assist with decision-making. First, *investigators* need to identify the institutional resources available to help decide the appropriate action, e.g. the IRB, the Ethics Committee, a research participant's advocate, the patient's personal physician. Second, the investigators and others involved in the deliberations should consider issues such as:

- Is the child old enough to provide assent?
- Are there creative strategies the investigators could implement in order to gain the child's cooperation?
- Does the study offer the prospect of direct benefit to the children enrolled?
- How severe is the child's fear? How insistent is he that he not be stuck?
- Is there a way to alleviate the child's fear so that he can participate without using *coercion* or *undue influence*?
- Could the child wait for a year or two and enroll in the study later (once his fear may have decreased)?

This is not an easy question because it does not have a clear "yes" or "no" answer.

Obtaining Informed Consent from Prisoners

Research involving *prisoners* requires approval by an IRB whose membership is specifically constituted to address the concerns of this vulnerable population per 45 CFR 46.304 (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.304*). If the research is conducted or supported by HHS, it must also be approved by the Secretary of HHS through the Office for Human Research Protections (OHRP). This approval signifies that "the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2)." (*http://www.hhs.gov/ohrp/policy/prisoner.html*)

The HHS regulations (45 CFR 46, Subpart C) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc*) require additional protections for prisoners who are involved as participants in research because they may "be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research."

The requirements specific to *informed consent* for prisoners are:

1. "Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired"
2. "Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole"

Community Consultation

In some cultures it is not appropriate to obtain *informed consent* **solely** from the individual participants, because the individual's interests may be considered to be intimately entwined with their community's interests. The appropriate way to attain community consent may vary widely, but is often achieved through meetings with large groups of community representatives or community leaders.

It is also appropriate to consult a community before conducting research when the research involves risk to discrete, identifiable populations. For example, members of a community may feel stigmatized if a number of members of that community participate in research that may reveal unpopular or dangerous traits.

Emergency Research

One example of a situation in which community consent is required is emergency research in life-threatening situations where obtaining *informed consent* is not feasible. In order for *investigators* to obtain a waiver of informed consent for emergency research, investigators must obtain consent from the communities in which the research will be conducted in addition to a number of other requirements. These requirements are described in Informed Consent Requirements in Emergency Research (*http://www.hhs.gov/ohrp/policy/hsdc97-01.html*).

Investigators should note that this **emergency waiver** of informed consent does not apply to research that falls under Subpart B (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb*) (*pregnant* women, human *fetuses* and *neonates*) or Subpart C (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc*) (*prisoners*) of the HHS regulations.

Respect for Persons: Summary

During the *informed consent* process, the principle of respect for persons is applied by requiring that all human subjects provide voluntary informed consent to participate in the research.

Practical application of this principle means that potential study participants must:

- Give their consent freely and voluntarily
- Have the decisional capacity to understand the information presented to them
- Be provided complete information about the study in order to make an informed decision

This module has examined:

- Information that should be included during the informed consent process
- The types of situations that can be considered for waiver of informed consent
- The appropriate involvement of *legally authorized representatives* for consent
- Obtaining consent from vulnerable populations, e.g. *pregnant* women, *prisoners* and *children*
- The need to undertake community consultation when the individual's interests are intimately entwined with their community's interests

Respect for Persons: Quiz

To take the quiz associated with this section. Go to the PHRP website (*http://phrp.nihtraining.com/*), and log in with your email address and password. Click on this section's main menu link.

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Beneficence

What This Module Covers:

- Risks and benefits
- Privacy and Confidentiality
- Institutional Review Boards (IRBs)
- Data and Safety Monitoring

The Objectives For This Module Are:

- To understand what aspects of research may constitute a benefit to research participants
- To identify possible risks to be considered in evaluating research
- To discuss methods to protect privacy of individuals and confidentiality of data
- To define the role of an IRB to ensure the rights and welfare of human subjects and
- To outline requirements for Data and Safety Monitoring for *clinical trials*

Beneficence

> *"Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term beneficence is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation."*
> *– Belmont Report*

Two general rules have been articulated as complementary expressions of beneficent actions:

1. Do no harm
2. Maximize possible benefits and minimize possible harms

Investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation.

Risk

Risk is the "probability that a certain harm will occur." [2]

All research involves some level of risk. We often think of risks in terms of physical harms that may occur as a result of participation in research protocols, but harms may also result from aspects of participation other than from research procedures. For example, harms may result from simply agreeing to be a participant in research, or they may result from disclosure of findings from a research study.

Most risks encountered by participants in research fall into the following categories: [3]

A. Physical

   Physical risks may include pain, injury, and impairment of a sense such as touch or sight. These risks may be brief or extended, temporary or permanent, occur during participation in the research or arise after.

2. Levine, RJ. 1988. Ethics and Regulation of Clinical Research, 2nd ed. New Haven: Yale University Press, p.37.

3. This list originated from: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: U.S. Department of Health and Human Services: Part C, section 2, "Assessment of risks and benefits" *http://ohsr.od.nih.gov/guidelines/belmont.html*.

B. Psychological

Psychological risks can include anxiety, sadness, regret and emotional distress, among others. Psychological risks exist in many different types of research in addition to behavioral studies.

C. Social

Social risks exist whenever there is the possibility that participating in research or the revelation of data collected by *investigators* in the course of the research, if disclosed to individuals or entities outside of the research, could negatively impact others' perceptions of the participant. Social risks can range from jeopardizing the individual's reputation and social standing, to placing the individual at-risk of political or social reprisals.

D. Legal

Legal risks include the exposure of activities of a research subject "that could reasonably place the subjects at risk of criminal or civil liability." [4]

4. 45 CFR 46.101 (b) (2) *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.101*

E. Economic

Economic risks may exist if knowledge of one's participation in research, for example, could make it difficult for a research participant to retain a job or to find a job, or if insurance premiums increase or loss of insurance is a result of the disclosure of research data.

Minimal Risk

Recall that the principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants. All research involves some degree of risk; however, some research is considered to be of *minimal risk*.

Minimal risk is defined in the Common Rule to be "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (45 CFR 46.102(i)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102*)

Types of Risk

Because research involves risks, *investigators*, Institutional Review Boards (IRBs), and other members of the research team must take responsibility for protecting participants against the risks of participating in research. Protections vary according to the kind of risk:

A. Physical

In many situations, physical risks in research can be minimized by carefully and skillfully following protocols, by having trained individuals conduct research procedures, through careful monitoring of research participants' health status, by recruiting appropriate populations, and by providing clinical care when needed.

B. Psychological

Possible ways to protect against psychological risks include reminding participants of their right to withdraw from research or limit their participation if they become uncomfortable, providing counseling or psychological support for participants who experience distress, or thoroughly debriefing research participants after research sessions are completed.

C. Social

Often, minimizing social risks to participants involves protecting confidential data, including not only the data collected, but the fact of participation in the research project itself.

D. Legal

Protections against legal risks often involve protecting the confidentiality of research data. For studies conducted in the United States, investigators can apply for Certificates of Confidentiality (*http://grants2.nih.gov/grants/policy/coc/*), which are intended to prevent investigators from being forced to disclose data that can be linked to identifiable research participants in legal proceedings.

E. Economic

Protecting confidentiality of data is one method for protecting against economic risks, such as those to employability and insurability. Investigators may elect to keep research data separate from medical records in order to prevent employers and insurance companies from obtaining information that could put the participants at risk.

Examples of Risk and Appropriate Protections

Risk Category	Risk Example	Protection Example
Physical	Fatigue	Supervision by physical trainer for signs or measures of fatigue beyond those defined as acceptable in the research protocol.
Social	Stigma	Investigators do not disclose identifiable data to research participant's co-workers.
Psychological	Anxiety	Friend or spouse can stay with participant during study procedures.
Legal	Disclosure of illegal drug use	Investigators increase protections for individual research participant's data from legal subpoena by obtaining a Certificate of Confidentiality.
Economic	Loss of job or advancement.	Investigators do not disclose information data to research participant's employer.

Designing Research: Anticipated Benefits Greater than Potential Harms

In general, the goal of research is to benefit society by contributing to generalizable knowledge about diseases, disorders, public health concerns, etc. Participation in research may:

- Benefit individual participants or communities
- Neither benefit nor harm individual participants or communities
- Pose risks to individual participants

The HHS regulations apply specifically to individual participants in research and require that:

- Risks are minimized
- Unavoidable risks are justified as necessary for sound scientific design
- Research studies are anticipated to make progress toward important, generalizable knowledge

Regulatory Requirement for Explaining Benefits and Risks

After minimizing risks to the extent possible, the HHS regulation requires that *investigators* consider:

1. **Protections against risks**: Where appropriate, investigators must describe procedures for minimizing potential risks, including risks to confidentiality, plans for ensuring any necessary medical or professional intervention, plans for data and safety monitoring for *clinical trials*, etc.
2. **Potential benefits to individual participants**: The proposed research has a favorable ratio of potential benefit to risk. This balancing act is often called a **risk-benefit analysis**
3. **Importance of the knowledge to be gained**: Investigators reasonably anticipate that the research will contribute to generalizable knowledge. This generalizable knowledge is considered a benefit to others, and risks to research participants must be reasonable in relation to the importance of the knowledge that reasonably may be expected to result

Compensation for Research Participation

Some types of research involve a significant commitment from research participants in terms of time or effort, and *investigators* may wish to provide *compensation*.

Institutions should consider establishing standards for fair and appropriate compensation.

During the *informed consent* process, investigators should explain to potential research participants:

1. If there will be compensation for their participation in the research
2. Appropriate expectations for receiving full, partial, or no compensation if research participants complete the study or withdraw prior to its completion
3. That compensation is meant to reimburse research participants for their time, research-related inconveniences and/or research-related discomforts

Compensation **is not** a benefit of the research.

Avoiding Undue Inducement

While the use of **inducements** to participate in research is considered appropriate under many circumstances, sometimes inducements can be unduly influential and inappropriate. These are referred to as **undue inducements**. As discussed in the **Respect for Persons** section, the level and kind of *compensation* must take into consideration the vulnerabilities of the research population to minimize the possibility of undue inducement.

"Undue inducements are troublesome because:

1. Offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and
2. They may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling — or continuing — as participants in a research project." [5]

Careful consideration of compensation is not only critical for beneficence, but may be critical for sound research. Considerations should include, but are not limited to,

5. Penslar, RL & Porter, JP; Office for Human Research Protections (OHRP). 2001. IRB Guidebook, 2nd ed.: Ch. III, Section G *http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm*

issues like participants' "medical, employment, and educational status, and their financial, emotional, and community resources." [5]

Avoiding the Therapeutic Misconception

Some research studies include examinations, diagnostic tests, and/or interactions with healthcare providers in addition to experimental interventions. These aspects of a research protocol may benefit participants by helping them to better understand a disease or condition, and may help in the participants' medical decision-making. While it is often appropriate to include treatment procedures in the conduct of research studies, there is a risk that research participants may misunderstand the benefits of research if they think that potential benefits of participation in research are certain. This is called the *therapeutic misconception*. Therapeutic misconception is the tendency for research participants to:

> *"... downplay or ignore the risks posed to their own well-being by participation ... (due to) the participants' deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit."* [6]

Investigators should discuss the risks and benefits of research as part of the *informed consent* process in order to minimize the possibility of therapeutic misconception.

6. Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.194.

Assessing Risks and Potential Benefits

Assessing risks and potential benefits is inexact, but *investigators* need to be able to explain to the funding agency, the IRB and the potential research participants how and why the potential benefits of research outweigh the risks of participating in a particular study.

The principle of beneficence requires that investigators consider a number of factors including:

- *Equipoise*
- Protecting the privacy of research participants and the confidentiality of research data
- Establishing oversight mechanisms to protect the rights and welfare of research participants and to determine the significance of the data

Equipoise and Importance of Knowledge to be Gained

A state of "*equipoise*" is required for conducting research that may pose risks to research participants.

For a *clinical trial* to be in equipoise, *investigators* must not know that one arm of a clinical trial provides greater efficacy over another, or there must be genuine uncertainty among professionals about whether one treatment is superior than another. [7]

Equipoise is essential for obtaining generalizable knowledge. If a clear and agreed-upon answer exists, asking research participants to assume the risks of research that will provide the same information is not acceptable; no new knowledge will be gained from the study.

7. Freedman, B. 1987. Equipoise and the ethics of clinical research. New England Journal of Medicine, 317(3):141-145.

Case Study: Equipoise in Research Involving Autistic Children

There are two standard treatments for autistic *children* who display a specific set of characteristics. One treatment is a cognitive behavioral intervention, and the other is a dietary and biomedical intervention. Both treatments have equally strong clinical evidence supporting their efficacy. A researcher proposes a comparison of the two interventions to determine which is preferable. The children will be randomized to one of two groups: half of the children will receive the cognitive behavioral intervention and the other half of the children will receive the dietary and biomedical intervention.

Is this study in equipoise?

Case Study: Equipoise in Research Involving Autistic Children

Is this study in equipoise?

There is insufficient data to persuade investigators or physicians that one approach is preferable to the other for a child displaying the specific characteristics.

This study is in equipoise.

Privacy and Confidentiality

Investigators are responsible for

- Protecting privacy of individuals
- Confidentiality of data

Privacy means being "free from unsanctioned intrusion." [8]

Confidentiality means holding secret all information relating to an individual, unless the individual gives consent permitting disclosure. [9]

8. "Privacy." 2004. The American Heritage Dictionary of the English Language, 4th ed. Boston: Houghton Mifflin Company.

9. *Modified from:* "Confidentiality." 2004. The American Heritage Stedman's Medical Dictionary. Boston: Houghton Mifflin.

Case Study: Confidentiality in Clinical Research

After the conclusion of a *clinical trial* in a small rural community, an *investigator* is anxious to publish findings. Understanding the NIH policies encouraging the reporting of demographic differences in intervention effect, and concerned about protecting the confidentiality of research participants, the investigator publishes only general demographic data such as sex, age, state, and county.

Is this an appropriate and acceptable way to protect the confidentiality of research participants?

Case Study: Confidentiality in Clinical Research

Is this an appropriate and acceptable way to protect the confidentiality of research participants?

Publishing demographic information is not acceptable in situations where the population is small or the disease/condition is rare because it is possible for research participants to be identified using only general demographic data.

For example, these protections were not sufficient after a hantavirus outbreak on an Indian Reservation in the United States. The information published made the identity of one of the individuals who died obvious to the local tribal leaders. In this case the published report not only compromised the identity of the research participant, it also violated the cultural taboo about not speaking of the recently deceased.

This is not an appropriate and acceptable way to protect the confidentiality of research participants.

Confidentiality

The need for maintaining confidentiality of private information exists in virtually all studies in which data are collected from or about living individuals. In most research, maintaining confidentiality is a matter of following some established practices, for example:

- Properly disposing of data sheets and other paper records
- Limiting access to identified data; and/or
- Storing research records in locked cabinets or secured databases

It may also be appropriate for *investigators* to remove direct identifiers from human specimens and data so that they may be analyzed without risk of accidental disclosure of private information. De-identifying data can be done in several ways, including *coding* and *anonymizing*.

Coded Private Information and Human Subjects Research

Research with coded private information or specimens involves human subjects if:

1. The private information or specimens were collected specifically for the currently proposed research project through an interaction or intervention with living individuals; or
2. The *investigator*(s) can readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Research with coded private information or specimens does not involve human subjects if:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Case Study: Research with Anonymized Data

You are an investigator proposing to use data from a colleague's database to conduct secondary analyses. You want to examine the behavior and attitudes in male spouses of female business executives. Your colleague will provide coded data for your proposed studies, and you and he enter into an agreement by which he will keep the key to the code and will have no other involvement in the research. Therefore, your colleague is not an *investigator* in your research.

Does this study involve human subjects?

Case Study: Research with Anonymized Data

Does this study involve human subjects?

The use of anonymized data means that the investigator cannot identify the individuals to whom the data pertain, and obtaining the data from a colleague with whom the investigator is not collaborating means that the colleague will not be able to link any research results to identifiable individuals.

Thus, the study does not involve human subjects because both criteria are met:

- The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain

Institutional Review Boards

Institutional Review Boards (IRBs) are specialized committees required by HHS regulations that safeguard the rights and welfare of human subjects. IRBs determine "the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice" (45 CFR 46.107).
(*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107*)

The major roles of IRBs in the oversight of research are:

1. Initial review and approval or disapproval of the proposed research activity
2. Ensuring that the proposed *informed consent* process meets all of the requirements of 45 CFR 46.116 (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*)
3. Providing continuing oversight for progress reports and protocols for ongoing research studies

IRB Membership

The HHS regulations (45 CFR 46.107) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107*) require that IRBs have at least 5 members from a variety of backgrounds. The experience, expertise and diversity of the IRB members should allow the IRB to provide a complete and adequate review of the research activities conducted at the institution.

Research may involve issues about which IRB members lack specific expertise. In these situations, IRBs should identify and invite individuals with specialized knowledge to assist in the review of applications and protocols where the expertise is required.

This issue was raised in the **Respect for Persons** section when discussing the HSS regulations for IRB membership when a study sought to enroll a vulnerable population (prisoners) in research (*http://phrp.nihtraining.com/beneficence/prisoners.php*). Another example where specific expertise may be needed is when a protocol proposes a study that will recruit participants presenting to a hospital Emergency Department (ED) with acute appendicitis. If the IRB lacks expertise about protections

for human subjects in emergency situations, the IRB Chair should ask an expert, such as the head of the ED to advise the IRB on the feasibility of the recruitment strategy.

Working with the IRB

Although IRBs and *investigators* have different roles in research, they have **a shared responsibility** to ensure that research participant protections are appropriate.

As an investigator, you will work most effectively with IRBs if you understand the information that the IRB needs in order to review and approve your proposed research study.

The HHS regulations provide **general criteria** for IRB approval of research, but the specific information that you need to submit may vary among institutions, and may even vary among IRBs at the same institution. You should contact the IRB or Research Administration office at your institution for specific instructions.

General Criteria for IRB Approval of Research (45 CFR 46.111)

- Risks to human subjects are minimized
- Risks to human subjects are reasonable in relation to anticipated benefits, if any, to human subjects and the importance of the knowledge that may reasonably be expected to result from the research
- Selection of human subjects is equitable
- *Informed consent* will be sought from each prospective research participant or the prospective research participant's *legally authorized representative* in accordance with and to the extent required by the HHS regulations (45 CFR 46.116) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*)
- Informed consent will be appropriately documented in accordance with and to the extent required by the HHS regulations (45 CFR 46.117) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.117*)
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the human subjects, and when appropriate there are adequate provisions to protect the privacy of human subjects and to maintain the confidentiality of data

Expedited IRB Review

Protocols may be reviewed either at a meeting of the full IRB or by "expedited review."

For "certain types of research involving no more than *minimal risk* and for minor changes to existing research," an IRB may choose to use an expedited review procedure (*http://www.hhs.gov/ohrp/policy/expedited98.html*). The expedited review may be conducted by the IRB chair or by designated experienced IRB member(s) (45 CFR 46.110) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.110*).

Investigators should understand that **expedited review** is conducted by fewer individuals, but is no less stringent and not necessarily faster than a **full IRB review**. If any individual reviewer who conducts an expedited review is unable to approve a proposed study, the study must be discussed by the full IRB.

Data and Safety Monitoring

Data and Safety Monitoring Plans describe protections for research participants and data integrity, and oversight for *clinical trials* at a level that is commensurate with the risks of participating in the clinical trial. That is, the method and frequency of monitoring is directly related to the possible harms to research participants in the clinical trial.

The HHS regulations require that studies involving human subjects should have a monitoring plan when appropriate (45 CFR 46.111) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111*).

The NIH requires that all clinical trials supported by NIH have a Data and Safety Monitoring (DSM) plan (*http://grants2.nih.gov/grants/policy/hs/faqs_aps_dsm.htm*).

Data and Safety Monitoring Boards

Appropriate protections and oversight can range from oversight by the Principal *Investigator* and IRB for a single-site, *minimal risk* clinical trial, to oversight by a full Data and Safety Monitoring Board (DSMB) and IRB(s) for a multi-site trial that involves greater than minimal risk.

DSMBs are committees of experts who have no bias with respect to the research and may be permitted to periodically view unblinded data and conduct interim analyses. Principal Investigators must not view unblinded data while their studies are ongoing because they need to maintain objectivity to the extent possible and to ensure integrity of the accruing data.

Case Study: Reducing Exposure to Mercury

An *investigator* proposes to work with the community organization of a population where many of the residents are exposed to high levels of mercury through occupational exposure. A previous study indicated that the harms resulting from exposure to a similar heavy metal contaminant could be mitigated through the use of a behavioral intervention. The investigators propose testing the intervention to see if mercury exposure can be reduced in this population. The research design involves randomizing human subjects either to the experimental behavioral intervention in addition to conventional therapy, or to conventional therapy alone. Should the behavioral intervention be determined to be successful, participants who received only conventional therapy will be offered the behavioral intervention after the completion of the study. Research participants will know which intervention they receive because conventional therapy does not include a behavioral component.

Does this study require a data and safety monitoring plan?

Case Study: Reducing Exposure to Mercury

Does this study require a data and safety monitoring plan?

A data and safety monitoring plan is required because the proposed study is a clinical trial.

Investigators are advised to refer to NIH Institute/Center policies and consult with NIH Program Staff in order to determine the appropriate method for data and safety monitoring.

Beneficence: Summary

The Belmont principle of beneficence involves maximizing possible benefits and minimizing possible harms to research participants.

Issues covered under Beneficence include:

- Protections against risks
- Definition of *minimal risk*
- Methods of weighing risks against anticipated benefits
- Potential benefits for the research participants
- The use of *compensation* for participation in research
- *Equipoise* and need for there to be genuine uncertainty about whether one treatment is superior to another
- Privacy & Confidentiality of research participants and research data
- Use of coded private information to protect confidentiality
- Use of an IRB to provide oversight for research involving human subjects
- Situations that allow for an IRB expedited review procedure
- Data and Safety monitoring for *clinical trials*

Beneficence: Quiz

To take the quiz associated with this section. Go to the PHRP website (*http://phrp.nihtraining.com/*), and log in with your email address and password. Click on this section's main menu link.

Since you have already read this section's content in the pdf, quickly click through each screen of the section until you reach the end. This allows the program to track and record your progress through this section. After clicking through all of this section's content, you will automatically be taken to the quiz.

The quiz is automatically scored when you submit the quiz form. If you complete the quiz with a satisfactory score, a check mark will appear next to the quiz score on the Main Menu screen. If you answer less than the required number of questions correctly, this section must be reviewed and the quiz retaken until a satisfactory score has been attained. You may retake the quiz only after clicking through each screen of the on-line section.

Justice

What This Module Covers:

- Fair distribution of the benefits and burdens of research
- Inclusion of Women, Minorities, and *Children* in Research
- Issues to consider in international research

The Objectives For This Module Are:

- To understand the concept of fair and equitable sharing of the benefits and burdens of research
- To learn about NIH policies on inclusion of women, minorities, and children in research

Justice

"Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects. "
–Belmont Report

The definition of justice has two parts:

- Fair procedures and outcomes are used to **select** research participants, and
- There is a fair distribution of benefits and burdens to populations who **participate** in research

Individual Justice and Social Justice

The Belmont Report distinguishes social justice and individual justice in the selection of subjects:

Individual justice requires that *investigators* "should not offer potentially beneficial research only to some patients who are in their favor or select only 'undesirable' persons for risky research."

Social justice "requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons."

More on Social Justice

"The choice of participants in research needs to be considered carefully to ensure that groups (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are not selected for inclusion mainly because of easy availability, compromised position, or manipulability." *10*

- These advancements are provided to those who can benefit from them, and
- The research should involve persons from groups who are likely to benefit from subsequent applications of the research

10. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: U.S. Department of Health and Human Services: Part B, section 3, "Justice." *http://ohsr.od.nih.gov/guidelines/belmont.html*

Equity vs. Equality in Human Subjects Research

The meanings of "equity" and "equality" are similar, but not the same. The difference between equity and equality has important implications for justice in research.

To treat "**equitably**" means to treat fairly;
To treat "**equally**" means to treat in exactly the same way.

Research should strive for equitable distribution of the risks and potential benefits of the research. This means that *investigators* are treating the groups

involved in the research fairly and justly. It does not necessarily mean that all groups are equally represented, but that their representation is fair and just based on the risks and potential benefits associated with the research.

Equitable Distribution

In order to achieve an equitable distribution of the risks and potential benefits of the research, *investigators* must determine the distribution of different groups (men and women, racial or ethnic groups, adults and *children*, age, etc.) in the populations that:

1. May be affected by the disease or condition under study, and
2. That are anticipated to benefit from the knowledge gained through the research

Challenges to Achieving an Equitable Distribution of Benefits and Burdens

Investigators must ensure that the participants recruited for the research will not be *unduly burdened* and that recruitment reflects the diversity of the population that may benefit from the knowledge generated from the study.

Individuals with the advantages of wealth and education may have an unfair advantage in terms of reaping the benefits of research because they may be able to afford new and costly treatments more easily than individuals in resource-poor settings.

NIH Inclusion Policies: Women and Minorities

One way the justice principle is applied is through the inclusion of women and minorities as participants in human subjects research. Because knowledge gained from clinical research may define health policy and shape standards of care for all patients, it is important to consider whether the intervention or therapy under scrutiny

"affects women or men or members of minority groups and their subpopulations differently."

The NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (*http://grants2.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm*) describes the Agency's requirements for the inclusion of women and minorities in NIH-supported biomedical and behavioral research involving human subjects.

Case Study: Migraine Intervention Trial

A researcher seeks to improve treatment for severe migraines that are partially responsive to oral medication. He proposes to test whether acupuncture, in addition to a sufferer's oral medication, is more effective treatment than oral medication alone. Because women are three times more likely to experience migraines than men (*http://www.ninds.nih.gov/disorders/migraine/migraine.htm*), he proposes to enroll three times as many women as men. They will be recruited from racially and ethnically diverse communities.

Does this study design fulfill the principle of justice?

Case Study: Migraine Intervention Trial

Does this study design fulfill the principle of justice?

The research includes women and men in proportion to the rates of severe migraines experienced by each sex, and is designed to have racial and ethnic diversity. The study provides both sexes and racial/ethnic communities with the opportunity for benefits from the *clinical trials*, and does not unfairly burden any single group with the risks of research. Its design is fair.

This study design does fulfill the principle of justice.

Case Study: Esophageal Cancer

A group of *investigators* proposes to investigate genetic factors that may increase risks for esophageal cancer. Genetic factors in esophageal cancer are not well understood and esophageal cancer occurs in many racial and ethnic populations. The investigators propose to collect DNA from cheek swabs and administer a risk factor questionnaire. Both cancer patients and age-matched controls will be included.

The investigators have access to a predominantly Caucasian sample, and have no plans to recruit participants outside of their available pool.

Is this an acceptable strategy?

Case Study: Esophageal Cancer

Is this an acceptable strategy?

The NIH inclusion policies require that inclusion be generalizable to the population of the United States. Acceptable inclusion of women and/or minorities depends both upon the scientific question addressed by the study and the prevalence of the disease, disorder, or condition in these populations.

In this case, it is scientifically appropriate to include a broad population. Failure to include groups that would be affected by this condition could result in gaps in scientific knowledge.

This is not an acceptable strategy.

Inclusion of Children in Research

NIH also applies the principle of justice through the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. (*http://grants.nih.gov/grants/guide/notice-files/not98-024.html*)

The policy emerged from the observation that children have often received treatments that have only been tested in adults, and that there is insufficient data on safe and effective uses for many treatments provided to *children*. Although the past practice of excluding children may have stemmed from good motives, "protecting" children in this way has resulted in:

1. Denying children the benefits of participation in research, and
2. Preventing the collection of sufficient data about the effects of agents in children

Excluding Children from Research

The NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (*http://grants.nih.gov/grants/guide/notice-files/not98-024.html*) states that *children* must be included in all NIH-supported human subjects research unless "… there are scientific and ethical reasons not to include them."

If an *investigator* proposes to conduct clinical research that does not include children, the exclusion of children must be fully justified using one or more of the exceptions described in the Policy.

Policy Exceptions

1. The research topic to be studied is irrelevant to children …
2. There are laws or regulations barring the inclusion of children in the research …
3. The knowledge is already available for children or will be obtained from another on-going study, and an additional study will be redundant …
4. A separate, age-specific study in children is warranted and preferable …
5. Insufficient data are available in adults to judge potential risk in children … in some instances, the nature and seriousness of the illness may warrant (children's) participation based on careful risk and benefit analysis ...
6. The study design is aimed at collecting additional data on pre-enrolled adult study participants …
7. Other special cases justified by the investigator and found acceptable to the review group and Institute Director

Definition of Children: HHS Regulations and NIH Policy

Although the HHS Regulations and the NIH Inclusion Policies apply to research involving children, they vary in their definitions of *children*.

HHS regulations

HHS regulations at Subpart D "Additional Protections for Children Involved as Subjects in Research" (45 CFR 46.402) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.402*) defines children as:

> *"Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."*

Thus for HHS regulatory requirements, the need for protections for "children" is defined by the location in which the study will take place and the research procedures. Research that involves children must follow the requirements for parental *permission* and child *assent* described in the HHS regulations at Subpart D. (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd*)

NIH Inclusion Policy

The NIH Policy and Guidelines on the Inclusion of Children as Participants in Research (*http://grants.nih.gov/grants/guide/notice-files/not98-024.html*) defines children as:

> *"Individuals under the age of 21."*

Additional information about the NIH Policy and Guidelines on the Inclusion of Children can be found at the Policy Implementation Page. (*http://grants2.nih.gov/grants/funding/children/children.htm*)

Research conducted or supported by the NIH must follow **both** the HHS requirements for protections and the NIH requirements for the inclusion of children.

Case Study: Selecting Populations to Include in Clinical Research

Below are a series of three different proposed clinical research studies and the appropriate population that should be used for each.

Match the appropriate population with the proposed clinical research below:

Clinical Research:	Populations:
Research on early diagnosis of senile dementia	A. Children only B. Children and Adults C. Adults only
Clinical trial comparing approved treatments for leukemia	
Experimental behavioral intervention to reduce bullying in elementary school classrooms	

Case Study: Selecting Populations to Include in Clinical Research

Match the appropriate population with the proposed clinical research below:

Research on early diagnosis of senile dementia

The appropriate population for this clinical research is adults only.

Senile dementias most commonly affect adults and it would not be appropriate to include *children* in research for which there is no clinical relevance.

Clinical trial comparing approved treatments for leukemia

The appropriate population for this clinical research is children and adults.

Since leukemia is a disease that can affect both *children* and adults, it is appropriate to include both populations in a *clinical trial* of approved treatments.

Experimental behavioral intervention to reduce bullying in elementary school classrooms

The appropriate population for this clinical research is children only.

An elementary school-based intervention would include whole schools or whole grades of children who, with parental permission, would participate in the research.

Justice and the Use of Placebos

The use of *placebos* in clinical research is relevant to all the issues addressed in this course. It raises issues related to justice, respect for persons, and beneficence. All three principles address a researcher's duty not to exploit or *deceive* research participants and to treat them fairly.

Risks associated with the use of placebos in research are:

Deception

Misleading research participants about the research purpose or procedures.

Therapeutic misconception

The tendency for research participants to: "downplay or ignore the risks posed to their own well-being by participation ... [due to] the participants' deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit."

The principle of Justice requires that when placebos are used, prospective research participants must be treated fairly. Unless justifications for a waiver are approved, the *informed consent* process must disclose sufficient information to ensure that potential research participants:

- Understand what placebos are
- Understand the likelihood that they will receive a placebo
- Are able to provide their fully informed consent that they are willing to receive a placebo

Justifying the Use of Placebos

Examples of justifications for the use of *placebos* include:

1. When there are no approved, effective treatments for the condition, or
2. If there is disagreement about whether standard treatment is better than placebo, or
3. When the additional risk posed by the use of placebo is minor and withholding the current standard therapy would not lead to serious or permanent harm, or
4. If the study is anticipated to result in widespread or major benefits and the receipt of placebo by individuals poses *minimal risk*

Incomplete Disclosure and Deception

Incomplete disclosure and *deception* may be useful for some research goals, but researchers may use them only after thorough consideration of:

- Whether the scientific goals of the research can be achieved by methods that do not involve incomplete disclosure or deception
- Whether participants would consider the information withheld during the *informed consent* process important to their decision to participate in the study
- Whether it is possible to inform participants that they will only learn about all the goals of the research after the research study is over

Waiver of Informed Consent

Incomplete disclosure and deception present challenges to justice because prospective participants' "*informed consent*" will not be fully informed. HHS regulations (45 CFR 46.116(d)) (*http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116*) allow informed consent to be waived only if:

- Participation in the research involves no more than *minimal risk*
- The waiver must not adversely affect the rights and welfare of research participants
- *Incomplete disclosure* or *deception* must be essential to the ability to carry out the research
- Whenever appropriate, research participants will be given additional pertinent information after they have participated in such a study (debriefing)

To Debrief or Not to Debrief

Debriefing of research participants after the study involves an explanation of the *deception* or *incomplete disclosure* of research goals to participants as well as a complete disclosure of the true goals of the research. Debriefing is generally considered to be appropriate, but must depend on whether the disclosure will result in harm.

Debriefing is appropriate when it will benefit the research participant's welfare (*http://www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm*) by:

- "… correct(ing) misperceptions, or
- reduc(ing) pain, stress, or anxiety concerning the (research participant's) self-perception or performance …"

Fairness in International Research

When HHS-supported research takes place outside of the United States questions about fair treatment and fair standards may arise. This may be especially true of research conducted in countries where:

- Resources may be scarce and/or
- Other vulnerabilities may be pronounced

A few of the many issues that demand careful consideration with respect to justice, as well as beneficence and respect for persons, include:

- How can research conducted in resource-poor setting avoid exploiting participants?
- What is owed to participants in clinical research and to the population of the host country after studies are complete?
- In addition to following the HHS regulations, what standards and assurances to protect research participants should *investigators* and non-US institutions use when conducting research abroad?
- How can regional or cultural differences be negotiated?
- For settings where cultural values impact *informed consent*, how should processes be altered?

Sustaining Benefits Locally

Investigators should think about how benefits to individual research participants and the local population may be sustained after the study is complete.

When planning a study, researchers and sponsors may:

- "… make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have proven effective for the participants …" [11]
- Consider how any effective treatment emerging from the research could be provided to the rest of the population

11. 2001. Ethical and policy issues in international research: clinical trials in developing countries, Vol. 1. Bethesda, MD: National Bioethics Advisory Commission, p.xi. *http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf*

Sustaining Benefits for Participants with HIV/AIDS in NIH-Supported Clinical Trials of Antiretroviral Agents

The NIH values continued treatment for research participants in HIV/AIDS antiretroviral studies.

> *"For antiretroviral treatment trials conducted in developing countries, the NIH expects* investigators*/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment."*

Information is found in the NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries (*http://grants.nih.gov/grants/policy/antiretroviral/*).

Standards and Assurances for International Research

The HHS Office for Human Research Protections (OHRP) has set the expectation that the HHS regulations, as well as any additional institutional and local standards (*http://www.hhs.gov/ohrp/international/*), will be followed in all research conducted or supported by HHS.

Investigators:

If you plan to engage in NIH-funded research in non-U.S. settings you must comply with the protections and standards set out in the HHS regulations Subpart A. Researchers may go beyond HHS regulations, however, to meet the ethical, legal, and social standards for the local setting.

Institutions:

Non-U.S. institutions engaged in HHS-conducted or -supported human subjects research must obtain an international (non-U.S.) Federalwide Assurance (FWA) (*http://www.hhs.gov/ohrp/assurances/assurances/index.html*) from OHRP.

IRB Review for Research in International Settings

Institutions have a profound responsibility to ensure that all IRBs designated under Federalwide Assurance possess sufficient knowledge of the local research context to satisfy the requirements for human subjects protections regardless of the IRB's geographic location relative to the institution and the research.

Knowledge of the local context may be provided by:

- Specialists with personal, direct knowledge of the local research context who participate in IRB discussions and provide insight on achieving protections for research participants
- An IRB situated within the local research context

Local Cultural Norms and Informed Consent

In unfamiliar settings, *investigators* should:

- Become familiar with local cultural norms and
- Seek guidance from community advisors and the IRB

Investigators should incorporate cultural norms into the research process whenever possible and appropriate. Examples of cultural norms include **community consent** and *informed consent* **from family representatives**:

- If **community consent** is the cultural norm, it may be appropriate to obtain community consent in advance of obtaining informed consent from individuals. Community consent cannot replace the informed consent from individuals.
- If cultural norms require permission from a family member before an individual may enroll in research, it may be appropriate to obtain permission from the family member in addition to informed consent from the prospective research participant.

Justice: Summary

Justice requires:

- Fair procedures and outcomes in the selection of research participants, and
- Distribution of benefits and burdens among the populations participating in research.

Individual justice requires that:

- Benefits of participation in research are offered to a diverse eligible population, and
- Risks of participation in research are shared by a diverse population

Social justice requires that consideration is given to classes of subjects that ought, and ought not, to participate in research. Considerations are based on:

- The ability of members of that class to bear burdens and
- The appropriateness of placing further burdens on already burdened persons.

This section also examines:

- Inclusion of women, minorities and *children*
- *Placebos*
- *Incomplete disclosure* and *deception*
- Debriefing participants after the study
- International research
- Research in resource-poor countries

This section also discusses the NIH guidelines regarding continued treatment for research participants in HIV/AIDS antiretroviral studies.

Justice: Quiz

To take the quiz associated with this section. Go to the PHRP website (*http://phrp.nihtraining.com/*), and log in with your email address and password. Click on this section's main menu link.

Since you have already read this section's content in the pdf, quickly click through each screen of the section until you reach the end. This allows the program to track and record your progress through this section. After clicking through all of this section's content, you will automatically be taken to the quiz.

The quiz is automatically scored when you submit the quiz form. If you complete the quiz with a satisfactory score, a check mark will appear next to the quiz score on the Main Menu screen. If you answer less than the required number of questions correctly, this section must be reviewed and the quiz retaken until a satisfactory score has been attained. You may retake the quiz only after clicking through each screen of the on-line section.

Conclusion

This course is designed to provide a minimum level of knowledge that an individual should have before designing a protocol for research involving human subjects.

There are numerous additional sources of training on this topic. Some are provided through:

- The NLM Bioethics Information Resources (*http://www.nlm.nih.gov/bsd/bioethics.html*) and through
- The HHS Office of Research Integrity RCR Resources — Human Subjects (*http://ori.dhhs.gov/education/products/rcr_humans.shtml*)

Further Training

You may wish to consult NIH staff and resources about research participant protections, such as:

- Scientific Review Officers
- Program Directors
- Specialized offices within the NIH Institutes/Centers
- The NIH Office of Extramural Research Human Subjects Web site (*http://grants.nih.gov/grants/policy/hs/index.htm*)
- NIH Grants Info: *grantsinfo@nih.gov*

You may also have access to resources at your institution or at nearby institutions, such as:

- IRBs
- IRB Administrators
- Experienced clinical investigators
- Hospital Ethics Committees
- Former research participants
- Advocacy groups
- Communities of potential participants
- Professional Societies

Staying Current

The material in this course will be updated periodically to reflect current issues.

Institutions and investigators that are using this Web-based training to meet the NIH requirement for Required Education in the Protection of Human Research Participants (*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html*) should check back at least once a year to be sure that your knowledge reflects the most current thinking on the various topics.

We welcome your feedback and suggestions on the material covered in this course.

Glossary

Anonymized data —

Lacking "identifiers or codes that can link a particular sample to an identified specimen or a particular human being."

Source: 2000. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance, Executive Summary. Rockville, MD: National Bioethics Advisory Committee, p. 2. (http://bioethics.georgetown.edu/nbac/hbm_exec.pdf)

Assent —

"...affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent."

Source: 45 CFR 46.402(b)

Autonomous person —

"An individual capable of deliberation about personal goals and of acting under the direction of such deliberation."

Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U.S. Department of Health and Human Services: Part B, section 1, "Respect for Persons" (http://ohsr.od.nih.gov/guidelines/belmont.html)

Children —

"Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

Source: 45 CFR 46.402(a)

Clinical trial —

"...a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)."

Source: US Department of Health and Human Services Grant Application (PHS 398) Part II: Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan (http://grants.nih.gov/grants/funding/phs398/phs398.pdf#page=109)

Coded data —

Identifiers are removed from the data in exchange for codes that correspond to the identifiers, and the identifiers are maintained separately from the rest of the dataset.

Coercion —

Influencing an individual's decision about whether or not to do something by using explicit or implied threats (loss of good standing in a job, poor grades, etc.).

Source: Faden, RR, and Beauchamp, TL. 1986. A History and Theory of Informed Consent. New York: Oxford University Press, p. 339.

Compensation —

May include money, other material compensation, such as a coupon or gift certificate, or other non-monetary rewards.

Deception —

Misleading research participants about the research purpose or procedures.

Delivery —

"Complete separation of the fetus from the woman."

Source: 45 CFR 46.202(b)

Diminished autonomy —

An individual with restricted capability of deliberation about personal goals and of limited ability to act under the direction of their deliberations.
Developed in contrast to the concept of the "autonomous person" in The Belmont Report.

Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, D.C.: U.S. Department of Health and Human Services: Part B, section 1, "Respect for Persons." (http://ohsr.od.nih.gov/guidelines/belmont.html)

Equipoise —

Substantial scientific uncertainty about which treatments will benefit subjects most, or a lack of consensus in the field that one intervention is superior to another.

Fetus —

"The product of conception from implantation until delivery."

Source: 45 CFR 46.202(c)

Incomplete disclosure —

Withholding some information in order to conduct an unbiased study, with the understanding that the information could be material to a decision by prospective participants about whether or not to participate in the study.

Informed consent —

A legally-effective, voluntary agreement that is given by a prospective research participant following comprehension and consideration of all relevant information pertinent to the decision to participate in a study.

Investigator —

"OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. Note that if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research."

Source: OHRP, HHS. 2004. Guidance on Research Involving Coded Private Information or Biological Specimens. (http://www.hhs.gov/ohrp/policy/cdebiol.html)

Legally authorized representative —

"An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."

Source: 45 CFR 46.102(c)

Minimal risk —

"The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Source: 45 CFR 46.102(i)

Neonates —

"A newborn."

Source: 45 CFR 46.202(d)

Permission —

"The agreement of parent(s) or guardian to the participation of their child or ward in research."

Source: 45 CFR 46.402(c)

Placebo —

An inactive intervention designed to resemble, as much as possible, its active counterpart in clinical research.

Pregnancy —

"Encompasses the period from the implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery."

Source: 45 CFR 46.202(f)

Prisoner —

"Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing."

Source: 45 CFR 46.303

Therapeutic misconception —

The tendency for research participants to: "downplay or ignore the risks posed to their own well-being by participation ... [due to] the participants' deeply held and nearly unshakeable conviction that every aspect of their participation in research has been designed for their own individual benefit."

Source: Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.194.

Undue burden —

Research populations must not be subject to undue burden, wherein they are "systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied."

Source: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: U.S. Department of Health and Human Services: Part B, section 3, "Justice" (http://ohsr.od.nih.gov/guidelines/belmont.html)

Undue influence —

"An offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance."

Source: Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.37.

Understanding Clinical Trials

Choosing to participate in a clinical trial is an important personal decision. The following frequently asked questions provide detailed information about clinical trials. In addition, it is often helpful to talk to a physician, family members, or friends about deciding to join a trial. After identifying some trial options, the next step is to contact the study research staff and ask questions about specific trials.

Frequently asked questions:

What is a clinical trial?

Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. ClinicalTrials.gov includes both interventional and observational types of studies. Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators.

Why participate in a clinical trial?

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research.

Who can participate in a clinical trial?

All clinical trials have guidelines about who can participate. Using inclusion/exclusion criteria is an important principle of medical research that helps to produce reliable results. The factors that allow someone to participate in a clinical trial are called "inclusion criteria" and those that disallow someone from participating are called "exclusion criteria". These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Before joining a clinical trial, a participant must qualify for the study. Some research studies seek participants with illnesses or conditions to be studied in the clinical trial, while others need healthy participants. It is important to note that inclusion and exclusion criteria are not

used to reject people personally. Instead, the criteria are used to identify appropriate participants and keep them safe. The criteria help ensure that researchers will be able to answer the questions they plan to study.

What happens during a clinical trial?

The clinical trial process depends on the kind of trial being conducted (See What are the different types of clinical trials?) The clinical trial team includes doctors and nurses as well as social workers and other health care professionals. They check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed.

Some clinical trials involve more tests and doctor visits than the participant would normally have for an illness or condition. For all types of trials, the participant works with a research team. Clinical trial participation is most successful when the protocol is carefully followed and there is frequent contact with the research staff.

What is informed consent?

Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study. If the participant's native language is not English, translation assistance can be provided. Then the research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

What are the benefits and risks of participating in a clinical trial?

Benefits

Clinical trials that are well-designed and well-executed are the best approach for eligible participants to:

- Play an active role in their own health care.
- Gain access to new research treatments before they are widely available.
- Obtain expert medical care at leading health care facilities during the trial.
- Help others by contributing to medical research.

Risks

There are risks to clinical trials.

- There may be unpleasant, serious or even life-threatening side effects to experimental treatment.
- The experimental treatment may not be effective for the participant.
- The protocol may require more of their time and attention than would a non-protocol treatment, including trips to the study site, more treatments, hospital stays or complex dosage requirements.

What are side effects and adverse reactions?

Side effects are any undesired actions or effects of the experimental drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental treatments must be evaluated for both immediate and long-term side effects.

How is the safety of the participant protected?

The ethical and legal codes that govern medical practice also apply to clinical trials. In addition, most clinical research is federally regulated with built in safeguards to protect the participants. The trial follows a carefully controlled protocol, a study plan which details what researchers will do in the study. As a clinical trial progresses, researchers report the results of the trial at scientific meetings, to medical journals, and to various government

agencies. Individual participants' names will remain secret and will not be mentioned in these reports (See Confidentiality Regarding Trial Participants).

What should people consider before participating in a trial?

People should know as much as possible about the clinical trial and feel comfortable asking the members of the health care team questions about it, the care expected while in a trial, and the cost of the trial. The following questions might be helpful for the participant to discuss with the health care team. Some of the answers to these questions are found in the informed consent document.

- What is the purpose of the study?
- Who is going to be in the study?
- Why do researchers believe the experimental treatment being tested may be effective? Has it been tested before?
- What kinds of tests and experimental treatments are involved?
- How do the possible risks, side effects, and benefits in the study compare with my current treatment?
- How might this trial affect my daily life?
- How long will the trial last?
- Will hospitalization be required?
- Who will pay for the experimental treatment?
- Will I be reimbursed for other expenses?
- What type of long-term follow up care is part of this study?
- How will I know that the experimental treatment is working? Will results of the trials be provided to me?
- Who will be in charge of my care?

What kind of preparation should a potential participant make for the meeting with the research coordinator or doctor?

- Plan ahead and write down possible questions to ask.
- Ask a friend or relative to come along for support and to hear the responses to the questions.
- Bring a tape recorder to record the discussion to replay later.

Every clinical trial in the U.S. must be approved and monitored by an Institutional Review Board (IRB) to make sure the risks are as low as possible and are worth any potential benefits. An IRB is an independent committee of physicians, statisticians, community advocates, and others that ensures that a clinical trial is ethical and the rights of study participants are protected. All institutions that conduct or support biomedical research involving people must, by federal regulation, have an IRB that initially approves and periodically reviews the research.

Does a participant continue to work with a primary health care provider while in a trial?

Yes. Most clinical trials provide short-term treatments related to a designated illness or condition, but do not provide extended or complete primary health care. In addition, by having the health care provider work with the research team, the participant can ensure that other medications or treatments will not conflict with the protocol.

Can a participant leave a clinical trial after it has begun?

Yes. A participant can leave a clinical trial, at any time. When withdrawing from the trial, the participant should let the research team know about it, and the reasons for leaving the study.

Where do the ideas for trials come from?

Ideas for clinical trials usually come from researchers. After researchers test new therapies or procedures in the laboratory and in animal studies, the experimental treatments with the most promising laboratory results are moved into clinical trials. During a trial, more and more information is gained about an experimental treatment, its risks and how well it may or may not work.

Who sponsors clinical trials?

Clinical trials are sponsored or funded by a variety of organizations or individuals such as physicians, medical institutions, foundations, voluntary groups, and pharmaceutical companies, in addition to federal agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), and the Department of Veteran's Affairs (VA). Trials can take place in a variety of locations, such as hospitals, universities, doctors' offices, or community clinics.

What is a protocol?

A protocol is a study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

What is a placebo?

A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the experimental treatment's effectiveness. In some studies, the participants in the control group will receive a placebo instead of an active drug or experimental treatment.

What is a control or control group?

A control is the standard by which experimental observations are evaluated. In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo.

What are the different types of clinical trials?

Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

Prevention trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.

Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.

Screening trials test the best way to detect certain diseases or health conditions.

Quality of Life trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

What are the phases of clinical trials?

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information

that will allow the experimental drug or treatment to be used safely.

In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

What is "expanded access"?

Expanded access is a means by which manufacturers make investigational new drugs available, under certain circumstances, to treat a patient(s) with a serious disease or condition who cannot participate in a controlled clinical trial.

Most human use of investigational new drugs takes place in controlled clinical trials conducted to assess the safety and efficacy of new drugs. Data from these trials are used to determine whether a drug is safe and effective, and serve as the basis for the drug marketing application. Sometimes, patients do not qualify for these controlled trials because of other health problems, age, or other factors, or are otherwise unable to enroll in such trials (e.g., a patient may not live sufficiently close to a clinical trial site).

For patients who cannot participate in a clinical trial of an investigational drug, but have a serious disease or condition that may benefit from treatment with the drug, FDA regulations enable manufacturers of such drugs to provide those patients access to the drug under certain situations, known as "expanded access." For example, the drug cannot expose patients to unreasonable risks given the severity of the disease to be treated and the patient does not have any other satisfactory therapeutic options (e.g., an approved drug that could be used to treat the patient's disease or condition). The manufacturer must be willing to make the drug available for expanded access use. The primary intent of expanded access is to provide treatment for a patient's disease or condition, rather than to collect data about the study drug.

Some investigational drugs are available for treatment use from pharmaceutical manufacturers through expanded access programs listed in ClinicalTrials.gov. If you or a loved one is interested in treatment with an investigational drug under an expanded access protocol listed in ClinicalTrials.gov, review the protocol eligibility criteria and inquire at the Contact Information number. If there is not an expanded access protocol listed in ClinicalTrials.gov, you or your health care provider may contact a manufacturer of an investigational drug directly to ask about expanded access programs.

For additional information on expanded access programs, please see the FDA website at Access to Investigational Drugs.

Expanded Access Studies can be found by in ClinicalTrials.gov:

1. go to the Advanced Search page,
2. select "Expanded Access Studies" from the "Study Type" pull-down menu, and
3. press Search.

or use these prepared links:

- Available Expanded Access studies
- All Expanded Access studies (available and no longer available)

Background Information

Last Updated: September 20th, 2007

Clinical Research Training

National Institutes of Health

Chapters:

1. **Ethical Issues in Human Research Subjects Research**
2. **Roles and Responsibilities of the Institution**
3. **Roles and Responsibilities of the Investigator**
4. **Regulatory Issues**
5. **Clinical Investigators and the Mass Media**

Adapted from the NIH Presentations found at http://crt.nihtraining.com/main_menu.php

What Makes Clinical Research Ethical?

Based on a presentation by Ezekiel J. Emanuel, M.D., Ph.D.

Test Your Knowledge

Before we discuss the details of what makes clinical research ethical, consider this question:

Is the following statement **True** or **False**?

Informed consent and IRB review are all you need to insure that human subject research is ethical.

Answer:

The statement is false: Informed consent and IRB review are all you need to insure that human subject research is ethical.

While informed consent and IRB review are both critical elements of ethical clinical research, they are only two requirements. Informed consent and IRB review alone do not constitute an ethical study. For example, how does informed consent and IRB review solve the ethical issues of clinical research in developing countries? The use of placebos? Phase I oncology research? Protection for communities? Using children in research? This module discusses the other elements that must be considered in conducting ethical clinical research.

Introduction – The Eight Ethical Requirements

The Eight Requirements

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair subject selection
5. Favorable risk-benefit ratio
6. Independent review
7. Informed consent
8. Respect for human subjects

In this section you'll see how ethical guidelines and regulations for human research studies have evolved and why it's important to consider several key requirements in research ethics.

When you complete this section you will:

- Understand the eight requirements that should be used when evaluating the ethics of clinical research studies
- Be able to justify those eight requirements
- Be able to apply the requirements to real clinical research studies.

This section, along with the quiz at the end, will take approximately 60 minutes to complete.

Introduction - Why do we need ethics standards?

When discussing why we need ethics standards, it is important to consider both the ethical and historical justifications.

The objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology. This objective requires human subjects who could be at risk of harm even as they are contributing to scientific knowledge. Human subjects are a necessary means to the end of greater knowledge. Consequently, because people can be used as a means, clinical research has potential for the exploitation of human subjects. Ethical guidelines are the main mechanism used to minimize the chances of exploitation of research participants.

Clinical Research + Human Subjects = *Potential for Exploitation*

The subject of ethics has been key to clinical research for over 100 years! History reveals strides in understanding the need for ethics standards as well as numerous ethical violations and scandals that caused controversy and required ethical guidelines.

National and international efforts to protect the rights and welfare of human subjects involved in research have occurred often in response to these ethical violations -- situations in which researchers were found to have ignored the fundamental rights of human subjects.

The following pages will take you through a brief history of clinical research and research ethics. As you peruse the past, keep in mind that the history of clinical research certainly justifies the need for ethics standards; however, even without the history, the ethical justification stands as reason enough.

A Brief History of Clinical Research

1747

Lind evaluates six different interventions on 12 sailors for the treatment of scurvy in the British navy. Lind tries each intervention on two sailors and the intervention that utilizes oranges and lemons leads to a cure for scurvy.

1776

Robertson observes the comparative efficacy of bark on the treatment of “continuous fever” aboard the British naval vessel, the *Juno*. When Robertson runs out of bark, sailors fare much worse.

1847

Semmelweis observes that women delivered by midwives had a much lower mortality rate than those delivered by obstetricians coming from the pathology theatre with germs all over their hands. He uses chlorinated lime juice to sterilize obstetricians' hands, preventing puerperal fever among women giving birth and reducing mortality.

1898

Fibiger, in Denmark, treats every other patient with anti-diphtheria serum in order to establish suitable controls.

1917

Comparative studies are conducted in Georgia to evaluate different diets to treat children with pellagra. The children are selected from orphanages. This study remains a classic in American history, illustrating the beginning of clinical research conducted on vulnerable populations: institutionalized children who can't defend their rights.

1931

The first randomized control trial appears to have involved TB patients in the United States. By the flip of a coin, half are selected to receive sanocryson and the others are controls.

“The patients themselves were not aware of any distinction in the treatment administered.”

1934

The first major collaborative trial occurs in Britain. Collaborating institutions in London, Edinburgh and Aberdeen evaluate serum to treat pneumonia.

1938

A placebo control [saline solution] is used for the first time in a trial examining the effectiveness of various cold vaccines.

1948

The first randomized, placebo-controlled trial of Streptomycin for TB published in the *British Medical Journal* stands as a landmark of modern clinical research.

While NOT the sole factor in determining the ethical treatment of human subjects, informed consent is highly integral to the process, and the history of informed consent brings to light even more justification for the need for ethical standards.

1767 Slater vs. Baker & Stapleton

The first recorded mention of informed consent occurs in a British lawsuit in 1767, Slater vs. Baker & Stapleton. According to the judges, “It appears from the evidence of the surgeons that it was improper to disunite the callous without consent: this is the usage and law of surgeons...”

This illustrates that the common practice among surgeons of the time was to get consent before performing procedures. There may be questions about the amount of information provided to patients and the quality of the informed consent, but the concept of attaining the patients' approval before initiating a major medical treatment is clearly the norm.

1892 Coley

Informed consent is not a modern phenomenon. Over 100 years ago physicians recognized the importance of informed consent in making clinical research ethical.

In 1892, Coley injects cancer patients to induce an immune reaction to see if that would lead to the destruction of the cancer. In one of his papers, Coley describes how he began treatment with a patient: “after some deliberation he consented” and only then injections began.

The inclusion of the need for deliberation and the patients' consent prior to the initiation of research procedures indicates that consent was expected in the practice of clinical research.

1897 Sanarelli and Osler

In 1897, the Italian researcher, Sanarelli claims to have discovered the bacillus of yellow fever. He also claims to have produced yellow fever in five patients by injecting them with the bacillus.

In 1898, after hearing of these experiments, Osler, the dean of American and International medicine, condemns Sanarelli's experiments in a scientific meeting by saying, “To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal.”

Osler's ability to say such a statement at a major scientific convention assumes that his fellow scientists in the audience accept obtaining patients' consent prior to conducting research as the ethical standard.

Obtaining informed consent from patients for research is neither a novel nor modern idea.

1901 Reed

In 1900, the United States Army establishes the Yellow Fever Board. In 1901, Walter Reed, chairman of the Yellow Fever Board, decides that the ethics of yellow fever research required five crucial elements:

1. Self-experimentation, meaning those on the board would be active subjects of the experiments
2. Written agreements with other subjects
3. Payment would be made to Cuban participants
4. Subjects would be restricted to adults only; no children enrolled
5. All journal articles describing patient enrollment would use the phrase “with his full consent.”

Once again, Reed's recognition of the need for these ethical standards establishes the understanding that ethics is critical to clinical research and the important role of informed consent.

1947 Nuremberg

In 1947, in the decision of the Nazi doctors' trial, comes the formulation of the Nuremberg Code. This code contains ten rules described in the judgment as “certain basic principles [that] must be observed in order to satisfy moral, ethical and legal concepts.” The first and longest principle states, “The voluntary consent of the human subject is absolutely essential.”

1964 Helsinki

The World Medical Assembly issues the Declaration of Helsinki in 1964. This declaration includes 22 recommendations “as a guide to every physician in biomedical research involving human subjects.” Subsequently, the document has now been revised five times: 1975, '83, '89, '96 and 2000. Its 6th revision is now in process.

1966 Beecher

In 1966, Beecher, then chairman of the Department of Anesthesiology at Harvard Medical School, writes an article in The New England Journal of Medicine. He delineates 22 examples in which patients “never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment, although grave consequences have been suffered.”

Included in Beecher's 22 examples are the following experiments:

1. Withholding of penicillin from US soldiers with strep throat, causing two cases of acute rheumatic fever and one case of acute nephritis.
2. Injecting live cancer cells into nursing home patients (Jewish Chronic Disease Hospital case)
3. Transplanting melanoma from a daughter who was dying of melanoma to her mother who died 451 days later of that very melanoma

Beecher emphasizes that these cases occur at the nation’s leading research institutions.

1972 Tuskegee

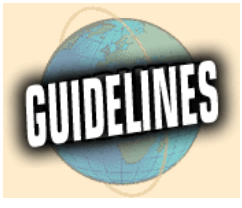
In 1932, the US Public Health Service begins a natural history study of untreated syphilis in Black males. Initially, 400 syphilitic and 200 uninfected controls are enrolled.

In the 1950s when penicillin becomes available to treat syphilis, the men do not receive the penicillin. Indeed, the Public Health Service actively attempts to prevent the men from receiving penicillin.

In 1972, in response to press reports, the Department of Health, Education and Welfare decides to stop the study.

Public outcry leads to the establishment of The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

International Guidelines



Violations of the rights of human subjects have led to guidelines for research on human subjects that extend beyond informed consent.

These guidelines are among those recognized as world standards. However, because they tend to be developed in response to specific events and scandals, each emphasizes certain ethical requirements and ignores others. In some cases, there are tensions among the different guidelines.

View some of the major **International Guidelines** with links to some of the various publications.

8 ethical requirements.

As noted, most of the international guidelines were developed in response to specific scandals. Thus, they do not present a general framework, but tend to focus, instead, on a single issue. However, by synthesizing traditional codes, the guidelines and relevant literature, we can delineate a framework of **eight principles for ethical human subjects research**.

These principles can be used to guide the ethical development, implementation and review of individual clinical protocols. This framework of ethical requirements is justified by widely recognized ethical values. They reflect how reasonable people would want to be treated. They represent the types of considerations that would be used to justify clinical research if it is challenged. They are meant to be universal and adaptable to different cultures, health conditions and economic settings. The remaining portion of "What Makes Clinical Research Ethical?" will briefly describe the Eight Ethical Requirements.

Eight Ethical Requirements

1. Collaborative Partnership

To be ethical, clinical research must involve the community in which it occurs.

This requires:

- Community participation in planning, conducting and overseeing research, and integrating research results into the health system
- Avoidance of supplanting existing health care services and sharing rewards with the community

Mechanisms to achieve collaborative partnership can be achieved by:

- Community advisory boards
- Patient advocates on scientific advisory boards
- Advocates for funding of research

2. Social Value

To be valuable, clinical research must lead to improvements in health or advancement in generalizable knowledge.

Valueless research includes the following:

- Non-generalizable knowledge
- A trifling hypothesis
- Results that are unlikely to be disseminated
- An intervention that cannot be practically implemented
- Substantial or total overlap of already proven results

Unfortunately, valueless research diverts resources, such as funds and personnel, from more worthy social pursuits and often exploits subjects, exposing them to potential harm without important resulting social or scientific benefit.

3. Scientific Validity

To be valid, research must:

- Be conducted in a methodologically rigorous manner that is practically feasible
- Have a clear scientific objective
- Be designed using accepted principles, methods and reliable practices
- Have sufficient power to definitively test the objective
- Offer a plausible analysis plan
- Be possible to execute
- Have an honest null hypothesis when comparing therapies

Invalid research includes underpowered studies, studies with biased end points, instruments, or statistical tests, and studies that cannot enroll sufficient subjects. Pilot studies in preparation for large scale trials are acceptable. If research doesn't result in data that is important and useable, then it places people at risk for no reason — it is invalid.

4. Fair Subject Selection

To select a human subject fairly, the following should be considered:

- The scientific objectives of a study usually will determine which subjects should be selected. Then minimizing risk, enhancing benefits and social value can be considered in selecting potential research participants
- Subjects should not be chosen merely because they are convenient
- Groups cannot be excluded without scientific reasons. For example, women as a class cannot be peremptorily excluded. However, higher risk is a valid reason to exclude certain groups
- Except under special circumstances, participating groups who are susceptible to the condition being researched and who assume risk, should benefit if the research provides a positive result, such as a new treatment

Fair subject selection helps ensure the following:

- Equals are treated fairly
- The benefits and burdens generated by social cooperation and activities such as clinical research are distributed fairly

5. Favorable Risk - Benefit Ratio

Clinical research can be justified only when it is conducted in a manner consistent with the standards of clinical practice. Risks to individual subjects must be minimized while the potential benefits must be enhanced. Overall, the potential benefits to subjects and society must equate to, or outweigh the risks.

The steps below discuss evaluating the risk / benefit ratio.

Steps:

1. Identify risks and minimize risks. Must consider physical, psychological, social and economic risks. But must not imagine or invent risks that are not present. Use procedures that are consistent with sound research design, that do not unnecessarily expose subjects to risk and, when appropriate, combine research procedures with diagnostic or treatment procedures already being performed on subjects.
2. Enhance potential benefits to individual subjects. Again consider physical, psychological, social and economic benefits. The benefit to society is assumed if research is already deemed to be socially valuable and scientifically valid. Extraneous benefits, such as payment or ancillary medical services, those not required for the research or safety of participants, are not considered when comparing the risks to benefit.
3. If potential benefits to the individual outweigh risks to the individual subject, then proceed. This would most likely apply in many phase II studies and all Phase III studies. In general, the more likely or severe the potential risk, the greater the likelihood or magnitude the prospective benefits must be.
4. If risks to the individual outweigh the potential benefits to the individual, then evaluate the risks against the social benefit of the knowledge gained. This issue arises most often in early phase studies. There is no formula for how potential social benefits should be balanced against the individual risks; however, when research risks exceed potential medical benefits to individuals and the benefit of useful knowledge to society, the clinical research is not justifiable.

6. Independent Review

Independent review helps to minimize the influence of potential conflicts of interest that you will encounter as a Principal Investigator and it also assures society that your study will not benefit from the abuse of your subjects.

As mentioned previously, you will have many goals that may conflict with each other as a Principal Investigator. Your goals include conducting high-quality research, completing your research expeditiously, protecting research subjects, obtaining funding and advancing your career.

Diverse interests can divert even the best-intentioned investigators. It can become easy to resort to shortcuts and convenience in research design, conduct and analysis. Independent review helps to minimize these potential conflicts.

Many people are aware of the Tuskegee incident and the atrocities that led to the Nuremberg Code. The nightly news tells the general public about incidents like deaths in gene transfer trials. That same public needs to be confident that abuses are not taking place in clinical research.

Independent review helps assure society that human subjects will be treated ethically. Review also assures the human subjects in clinical research that the trial is ethically designed and the risk-benefit ratio is favorable.

In the United States, independent review is conducted by a number of groups, including granting agencies, local Institutional Review Boards (IRBs) and data and safety monitoring boards (DSMBs). Importantly, the need for independent review does <u>not</u> imply the need for multiple reviews at each institution where the research is being conducted.

7. Informed Content

Informed consent is an ethical requirement for the following reasons:

- It shows respect for your subjects' autonomy
- Informed consent lets individuals decide whether they want to be subjects in a clinical trial, participating only when the research is consistent with their values, interests and preferences
- For those who cannot consent, such as children and mentally impaired subjects, research must fit with their interests

Informed consent requires:

- Competence of the subject
- Disclosure of relevant information to the subject
- Understanding of the information by the subject
- Voluntary (uncoerced) decision-making by the subject

A truly informed consent means that human research subjects have been accurately informed of the purpose, methods, risks, benefits and alternatives to the research.

They must understand the information and its impact on their own clinical situation.

Federal regulations require eight elements be included in each informed consent document. They are as follows:

- Purpose and duration of participation
- Risks

- Benefits
- Alternatives
- Voluntariness and right to withdraw without penalty
- Confidentiality of records
- Compensation for injuries
- Person to contact for answers to questions

8. Respect for Human Subjects

The ethical requirements for clinical research does not end when subjects sign the informed consent document. Ethically, respecting your subjects is a top priority. You are required to respect both their autonomy and their welfare.

Specifically:

- Monitor their welfare and provide appropriate treatment for adverse events
- Demonstrate your respect by protecting their confidentiality
- Permit them to withdraw without penalty
- Provide your subjects with new information, even after they are enrolled, such as information about new risks
- Finally, inform your subjects of what was learned from the research

Another of the requirements to respect subjects at the NIH involves educating subjects about Advance Care Directives. Introducing and discussing the directives with subjects are the responsibilities of the Principal Investigator, and it's important to remember that these directives are not just about treatment for someone who is terminally ill and becomes incompetent.

The **NIH Advance Care Directive** permits the following:

1. The designation of a substitute decision maker or proxy
2. The specification of preferences for participation in research
3. The specification of preferences for end-of-life care

8 ethical requirements.

To conclude, the Eight Ethical Requirements for using human subjects in clinical research are as follows:

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair Subject Selection
5. Favorable Risk-Benefit Ratio
6. Independent Review
7. Informed Consent
8. Respect for Human Subjects

All eight of the requirements are necessary and essential to make clinical research ethical. Researchers are obligated to fulfill all eight.

In some cases, informed consent may be waived. For instance, in emergency research, an advance directive consent may be used.

As you consider the importance of these ethical requirements keep the following three statements in mind:

1. All eight ethical requirements should be applied to all research
2. The requirements are designed to be universal and to represent the way reasonable people want to be treated
3. Ethical requirements have been developed in response to historical mistreatment of human research subjects

Who Can Help?

The following types of people can help you assess your research for the eight ethical requirements:

1. **Investigators** can help assess value, validity, fair subject selection, favorable risk-benefit ratio, informed consent and respecting subjects
2. **Statisticians** can help assess validity, favorable risk-benefit ratio, and independent review
3. **Ethicists** can help assess value, fair subject selection, favorable risk-benefit ratio, informed consent, independent review, and respecting subjects
4. **Lay people** can help assess value, favorable risk-benefit ratio, informed consent, and respecting subjects
5. On the next screen, you'll be challenged to determine the ethical requirements especially relevant to two case studies.

Real Life Research Studies

Click on the real-life research studies below to learn more about them and assess them for the eight ethical requirements.

To Placebo or Not to Placebo, That is the Question!

A new class of antiemetics, serotonin antagonists were developed in the late 1980s. To evaluate these drugs, investigators conducted placebo-controlled trials randomizing cancer patients receiving emetogenic chemotherapy to either placebo or the serotonin antagonists. At the time, the dominant antiemetic therapies were partially effective. However they were not completely effective, especially for strongly emetogenic chemotherapy, and had some significant adverse effects, especially dystonic reactions.

Alternative antiemetic therapies with fewer adverse effects were viewed as desirable. The placebo-controlled trials included “rescue” medication if patients had persistent nausea or vomiting. Is a placebo arm ethical in this case?

Assess this Research for the Eight Ethical Requirements

Check the **four** ethical requirements especially relevant in determining if randomized control trials of RRV-TV vaccine should continue in developing countries.

- [ ] Collaborative Partnership
- [ ] Social Value
- [ ] Scientific Validity
- [ ] Fair Subject Selection
- [ ] Favorable Risk-Benefit Ratio
- [ ] Independent Review
- [ ] Informed Consent
- [ ] Respect for Human Subjects

While all eight ethical requirements needed to be fulfilled in regard to determining the use of a placebo arm, the following areas were particularly important:

Social Value

There was no social value in knowing whether the serotonin antagonists were better than placebo in controlling emesis, since placebo was not the standard of care. Even if the serotonin antagonists were shown to be more effective than placebo, it was not known how they would compare with extant interventions in effectiveness and adverse-event profile. Thus a placebo-controlled trial does not fulfill the value requirement.

Scientific Validity

Ethical and scientifically valid randomized trials require an honest null hypothesis. In this case, the serotonin antagonist was not equivalent to the placebo. In fact, randomized controlled trials with serotonin antagonists vs. active antiemetic therapy were being conducted. Thus, a placebo-controlled trial was not the only scientifically valid method.

Risk-Benefit Ratio

The inclusion of "rescue" medication indicates there was an alternative standard treatment for chemotherapy-induced emesis and that emesis was sufficiently harmful to require intervention. Permitting patients to vomit while being administered placebo causes them unnecessary harm. Thus, a placebo-controlled trial of antiemetics for chemotherapy-induced emesis does not minimize harm in the context of good clinical practices. Therefore it fails the favorable risk-benefit ratio when an available clinical intervention can partially ameliorate some of the harm.

How Many Deaths are Too Many?

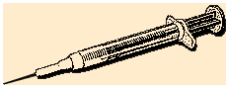
Another controversial issue involves research in developing countries. Recently, a rhesus rotavirus tetravalent (RRV-TV) vaccine was licensed in the United States after randomized trials demonstrated a 49% to 68% efficacy in preventing diarrhea and up to 90% efficacy in preventing severe cases of diarrhea.

However, shortly after approval, the vaccine was withdrawn from the US market because of a cluster of cases of intussusception, representing an approximately I in 10,000 added risk of this complication.

Should randomized controlled trials of RRV-TV vaccine proceed as planned in developing countries or wait for a new vaccine candidate to be developed?

Assess this Research for the Eight Ethical Requirements

Check the **three** ethical requirements especially relevant in determining if randomized control trials of RRV-TV vaccine should continue in developing countries.



- [ ] Collaborative Partnership
- [ ] Social Value
- [ ] Scientific Validity
- [ ] Fair Subject Selection
- [ ] Favorable Risk-Benefit Ratio
- [ ] Independent Review
- [ ] Informed Consent
- [ ] Respect for Human Subjects

BEST ANSWERS:

While all eight ethical requirements need to be fulfilled in regard to determining whether or not to continue the RRV-TV vaccine trials, the following areas are particularly important:

Social Value

Despite oral rehydration therapy, more than 600,000 children in developing countries die annually from rotavirus diarrhea. In some countries, the death rate from rotavirus is nearly 1 in 200. Clearly, a rotavirus vaccine with even 80% efficacy that prevented more than half a million deaths would be of great value. But is research using the RRV-TV vaccine ethical when the risk of intussusception stopped its use in the United States? The RRV-TV vaccine was the first and only licensed rotavirus vaccine and has already been administered to nearly 1 million children; potential alternative rotavirus vaccines are still years away from Phase III research. Thus, given the potential benefit of preventing deaths from rotavirus in developing countries, a trial of RRV-TV vaccine now--even if a better vaccine becomes available in a few years--is worthwhile. There is value to the research on the vaccine for developing countries only if there is reasonable assurance children in the country would be able to obtain it if it proved effective.

Scientific Validity

Vaccines effective in developed countries may or may not be as effective or safe in developing countries. Host, viral, and environmental factors and seasonality of the disease can alter the efficacy and safety profiles of a vaccine. Thus, there is good scientific rationale for determining whether the RRV-TV vaccine can achieve sufficient levels of protection against diarrhea with an acceptably low incidence of complications in children in developing countries. In this case, given the lack of an established method of preventing rotavirus infections in these countries, a placebo-controlled trial would be valid.

Fair Subject Selection

Two factors suggest that, in the RRV-TV vaccine study, subjects in developing countries are being selected for reasons of science and not being exploited. First, the most appropriate subjects for a rotavirus vaccine trial are infants and children who have a high incidence of rotavirus infection and who experience significant morbidity and mortality from the infection. In such a population the efficacy of the vaccine would be most apparent. Second, since the RRV-TV vaccine has been withdrawn from the US market, children in developing countries are not being selected to assume risks to evaluate a vaccine that will ultimately benefit children in developed countries. As long as the RRV-TV vaccine would be made available to the population recruited for the study if proven safe and effective, children in the developing countries are being selected appropriately.

Risk–Benefit Ratio

The final element is evaluation of the risk-benefit ratio. In the United States, the RRV-TV vaccine posed a risk of intussusception of about 1 in l0,000, while rotavirus causes about 20 deaths annually or in fewer than 5 in 1 million children. Thus, in developed countries the risk-benefit ratio is not favorable -- 1 death from rotavirus diarrhea prevented at the risk of 20 to 40 cases of intussusception. Because of underlying disease burden, the risk-benefit ratio in developing countries is much different. If rotavirus causes the death of 1 in 200 children while the RRV-TV vaccine causes intussusception in 1 in 10,000 children, about 50 deaths from rotavirus diarrhea are prevented for each case of intussusception. Consequently, the risk-benefit ratio of the RRV-TV vaccine is favorable for individual subjects in developing countries while it is unfavorable for subjects in developed countries. This difference in risk-benefit ratios is a fundamental part of the justification for conducting the research on an RRV-TV vaccine in a developing country when it could not be ethically conducted in a developed country.

Conclusion

To conclude this section, take a look at some actual questions posed by Principal Investigators to Dr. Emanuel at the end of his live presentation of this material. Click on the questions to view Dr. Emanuel's answers.

How do you handle a situation in which your research affords only benefits to society and none to your human subjects?

QUESTION: "I can see in some cases where there are no conceivable benefits to the patient even though the patient is pretty far advanced in their dying, so it is possible that there is no benefit to the patient, but yet there might be benefit to society. Would you clear that situation up ethically?"

ANSWER: "As I mentioned previously, the four-step procedure for evaluating favorable risk-benefit ratios does address situations in which the risk-benefit ratio is such that the risks to the individual subject outweighs the benefit. There may be benefits to the individual but the study is very risky, or there may be no benefits whatsoever. This is included in the fourth step. "Being an oncologist, I have enrolled numerous patients in Phase I studies that are classically 'No Benefits' studies. Yes, these kinds of studies can be ethical. Under what circumstances are they ethical? If the scientific knowledge gained from the studies is truly valuable, not just because it is research, but because the research is justifiably valuable to society in terms of generalizable knowledge that will lead to improved healthcare. 'No Benefit' studies can be ethical, but it does not happen by coincidence; it happens by design."

Is the issue of fair subject selection one of not excluding subjects or one of actively working to include all representative groups?

QUESTION: "Regarding the fair subject selection issue: it seems there's some confusion about not excluding subjects versus working actively to ensure that subjects of all representative groups are included. Sometimes that comes in conflict with perhaps the validity rule, and the 'practically feasible' issue. You may only have the sources to do the study at one hospital, which will not have an ethnically balanced composition. You know, there may not be very many Native Americans in downtown Washington, so would you comment on that conflict? Also, how does this issue relate to the risk-benefit ratio and the cost-benefit ratio?"

ANSWER: "The Eight Ethical Requirements can conflict when researchers try to satisfy all of them. Part of the issue and responsibility of an investigator, and part of the issue and responsibility of the IRB, is to see when they do conflict and determine how to adjudicate them."

"Conflicting ethical requirements are a common occurrence in daily life: 'My duty to this person, My duty to family, My duty to other people.' Most people have intuitive ways to balance this out. The same thing happens in clinical research."

"By laying out these eight ethical principles, I am not suggesting that they won't conflict with each other."

"To address the topic of active patient recruitment, it is important to ask the question, 'Why is recruitment an integral part of clinical research?' In this country, unfortunately, there is a tendency to actively exclude the very people who are targeted for the treatment if it works and gets approved. For example, women have received drugs or procedures that have only been proven to work on men and children have received drugs that have only been tested on adults."

"Part of the social value of research, therefore, must include, 'How widely will this drug or procedure be used?' And therefore, part of the scientific validity is, 'Does the research include the right populations for the desired social value?' In theory, these principles must be balanced."

"Keep in mind that Phase I studies don't require every representative group in order to test an hypothesis. However, Phase II and Phase III studies are different. As it becomes apparent that the research is going to work and be generalizable to a wide population, it becomes more incumbent upon the researcher to assure that the population that will ultimately be affected is also reflected in the clinical research trial."

"These eight principles are not meant to eliminate tough cases. Researchers are going to have tough cases, and they must consider all of the principles as their research evolves."

What are the vulnerability issues surrounding a patient without insurance, who needs a transplant and can only get it by participating in the NIH's IRP?

QUESTION: "An issue somewhat unique to the NIH is the issue of patient vulnerability in terms of choosing between coming to the NIH and being a research subject versus getting no care because of no insurance. This comes up repeatedly with our transplant protocol. These patients are really choosing between having their transplants here or no transplant. How would you factor that into risk-benefit analysis?"

ANSWER: "I would not factor that into risk-benefit analysis. Actually, I'm very comfortable with that situation under the following circumstances: If the research is approved as socially valuable and scientifically valid, and there is a favorable risk-benefit ratio, and the uninsured are not the only subjects being recruited then the main concern is about potential undue inducement. This is not undue inducement of the researcher to the subject, but socioeconomic injustice on this individual. My own view is that if the research passes the first five requirements, I'm less worried about socioeconomic injustice because the whole protocol is ethical, the uninsured are not the only subjects being targeted, and the risk-benefit ratio is favorable."

"Let me take another example. When I was a practicing oncologist at the Dana Farber Cancer Institute in Boston, there was the NSABP tamoxifen chemo-prevention trial. I was asked to see a woman who was mentally retarded and who was at high risk for developing breast cancer. Every woman in her family had had breast cancer and she had lobular carcinoma-in-situ (LCIS). She could not consent. The question posed to us was , 'Should we enroll her in this trial testing tamoxifen?'"

"There was a big controversy about it. I felt completely comfortable enrolling her. We were not targeting only the mentally incompetent. As a matter of fact, the single largest group being enrolled were female nurses and health care professionals. The study was socially valuable, scientifically valid and had a favorable risk-benefit ratio."

"As long as you're sure the trial is ethical and the uninsured are not the only people being targeted, then enrolling the uninsured even if they have few options is ethical."

Does a research protocol have to go through the IRB in addition to independent review?

QUESTION: "Does that mean that it has to go through the IRB in addition to independent reviewers outside the NIH, or did you just mean ...?"

ANSWER: "Independent Review means IRB review. Different institutes and different institutions around the country have different ideas about independent review. Some require a scientific review before the protocol gets to the IRB and some find the IRB satisfactory."

"We use the phrase Independent Review only because many other countries do not call their review boards IRB's. They're called Research Ethics Committees. There's no lock on the term IRB. That just happens to be the American term, not the universal designation for independent review."

How important is it to communicate with former research subjects about the progress and results of a clinical trial?

QUESTION: "How important is it to communicate with former research subjects about the progress and results of a clinical trial?"

ANSWER: "It is important."

"My last major study involved 988 terminally ill patients and their care-givers, and it's difficult to know how to keep in contact with them. Imagine 10,000 people enrolled in an epidemiology study. Informing them of the results of the research is a formidable task."

"Many NIH patients come here frequently and enroll in study after study. Determining a way to inform them and keep them up-to-date is an aspiration worth the effort. Subject after subject comes here and tells us that they have no idea what happened with the result of the study they participated in, and they wish they knew. Improving communication with our current and former patients is an important task that deserves more attention."

What would be the legality of having a Web site available to people interested in following the study results?

QUESTION: "What would be the legality of having a Web site available to people interested in following the study results?"

ANSWER: "I am not a lawyer. I usually never comment on the law unless I really know something about it, and in this case I know nothing about it. Probably it would be a fine way of keeping them up to date as long as you don't have personal and individual identifiers there, especially if you're going to publish that data eventually."

Should patients enrolled in a study have access to the annual review of that protocol?

QUESTION: "I'm not suggesting this, but merely raising the possibility. Do you think that the patients enrolled in the study should have access to the annual review of that protocol?"

ANSWER: "It is probably not a good idea for the patients enrolled in a study to have access to the annual review. There is a good deal of information in annual review documents that would create unnecessary anxiety and thus make it inappropriate for review by patients."

"I think most people simply want to know what was learned from the study they participated in; what was the social benefit to science."

"In this regard, we're appealing to their altruism rather than merely to their self-interest. And I think that we ought to encourage that kind of motivation in research subjects."

Are there major or significant differences between the U.S. policies and procedures and those in other countries where clinical research is performed?

QUESTION: "Are there major or significant differences between the US policies and procedures and those in other countries where a lot of clinical research is performed?"

ANSWER: "There should not be differences in the eight basic principles, but there will be differences in how they are applied in particular, how cases / conflicts are resolved, and which principles to give emphasis to."

"For example, there are many disagreements about the information that should or should not be included in the informed consent document, and the appropriate length the document."

"Also, the risk-benefit analysis tends to be somewhat of a judgment call and different committees, even within the same countries, make different evaluations on these kinds of issues."

What is the PI's responsibility in assuring the eight elements of the federal guideline for protocols are adhered to in an offsite investigation?

QUESTION: "What is the PI's responsibility in assuring, let's say, the eight elements of the federal guideline for protocols be adhered to in an offsite investigation?"

ANSWER: “Let me say two things. First, I have not focused on federal regulations because I want to present a broader means for thinking about the ethics of clinical research. The federal regulations deal with a very narrow range of what I have presented. They do not focus in on the whole.”

“Second, in some multi-site research, there is someone above the PI who is overseeing all the other sites, but when the PI is responsible for the whole study, it creates a different set of responsibilities. In this case, the PI has supreme authority. The buck stops with the PI.”

When you’re finished exploring these questions, click the Next button below to proceed to the test questions for this section.

Roles and Responsibilities of the Institution

Based on a Presentation by and on a Course authored by Alison Wichman, M.D.

Test Your Knowledge

Before we discuss the NIH's role regarding human subjects research, test your knowledge by answering the following question:

Which of the following is the most important protection for people participating in research protocols?

A. Informed consent documents
B. Investigators who understand and appreciate their responsibilities and those of the institution in protecting human subjects
C. Strictly enforced regulations
D. International guidelines for good clinical practice

An**swer:** Which of the following is the most important protection for people participating in research protocols?

A. Informed consent documents
B. **Investigators who understand and appreciate their responsibilities and those of the institution in protecting human subjects**
C. Strictly enforced regulations
D. International guidelines for good clinical practice

The correct answer is b**.**

Investigators who understand and appreciate their responsibilities and those of the institution are the most important protections for human research subjects.

Informed consent, regulations and guidelines are important safeguards to the safety, rights and welfare of human subjects. These safeguards are more likely to be implemented when research institutions have clear policies and procedures related to the conduct of clinical research and their investigators understand, appreciate and apply them to their research activities.

Introduction

During this portion of your clinical research training, you will learn the role of the NIH, as an institution, in protecting human subjects in the NIH's Intramural Research Program (IRP). This section covers the following topics:

- The institutional requirements of the NIH when investigators in its IRP conduct research involving human subjects
- The role of the NIH's Institutional Review Boards (IRBs) in protecting human research subjects and tips to help you work effectively with them
- How to think methodically about the human subject protections aspects of your research protocols

This section, along with the quiz at the end, will take approximately 90 minutes to complete.

Like all American research institutions, the NIH is held to societal, governmental, institutional and professional standards in protecting human research subjects. Because the American taxpayer supports research conducted by the NIH, our responsibility to American society is strong.

The current ethical principles and U.S. regulations governing research involving human subjects were a product of national necessity. In the 1950s, 1960s and 1970s reports surfaced in lay and professional presses concerning some research studies which infringed on the rights of the participants and, in some cases, harmed them.

Society's confidence in clinical researchers was shaken. There was general consensus that if U.S. researchers were granted the privilege to conduct research involving people, ethical guidelines and laws needed to be put into place to assure that the rights and welfare of subjects were protected. These concerns led to congressional passage of The National Research Act in 1974.

The Evolution of Ethical Principles and Federal Regulations

This act led to formulation and publication of The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This report was a major advance in the development of public policy. It provided guidance for distinguishing therapeutic medicine from research, identified three fundamental ethical principles for the protection of human subjects, and illustrated how the ethical principles should be applied to the conduct of human subjects research.

In 1981, the ethical principles of the Belmont Report were incorporated into Title 45, Code of Federal Regulations, Part 46, Protection of Human Subjects (45 CFR 46) issued by the Department of Health and

Human Services (DHHS). Initially these regulations were applicable only when research was supported or conducted by DHHS, but in 1991 45 CFR 46 was revised and became the basic policy that now governs all federally sponsored research (referred to as "The Common Rule").

The Evolution of Ethical Principles and Federal Regulations

Failure to Comply = loss of privilege to conduct research involving human subjects.

Our society has granted researchers a conditional privilege to conduct research involving people. The condition is that the rights and welfare of the subjects take precedence over the advance of knowledge through research.

As an NIH IRP you are expected to understand the ethical principles underlying your clinical research activities, comply with federal regulations and NIH policies and procedures related to clinical research.

In order to help you, the NIH IRP has organized a Human Research Protection Program (HRPP) which includes policies and procedures, educational activities for you and other researchers, and review of your research activities by Institutional Review Boards (IRBs).

Overall responsibility for the NIH's HRPP rests with the Deputy Director for Intramural Research (DDIR).

The chart below illustrates the NIH's institutional responsibilities for human subjects protection and defines its relationship to you, as a researcher, society and federal agencies such as the Department of Health and Human Services and the Food and Drug Administration.

Click on the three outer sections of this chart to view more information.

Institutional Responsibilities

- Institution (NIH) — DDIR is Dr. Michael Gottesman
    - Maintains the NIH Office of Human Subjects Research (OHSR)
    - Educates researchers about IRP policies and procedures
    - Establishes policies and procedures for NIH IRP
    - Establishes and educates IRB's
- Federal Agencies (DHHS & FDA)
    - Establishes ethical principles
    - Establishes federal regulations
    - Oversees the protection of human subjects through DHHS's Office of Human Protection (OHRP)
- Society
    - Conditional Privileges: right and welfare before research

The NIH Intramural Research Program (IRP)

FWA - Standards

Now we will focus on some of the institutional procedures the NIH has put into place to help you fulfill your responsibilities. Two key NIH documents about which you should be knowledgeable are:

- Standards for Clinical Research Within the NIH Intramural Research Program
- The NIH Federal Wide Assurance (FWA)

Standards for Clinical Research Within the NIH Intramural Research Program

These standards were developed by the Clinical Center Medical Executive Committee and published in January 2000 to assure high quality research and safety of research subjects in all NIH clinical research. The standards address six areas related to conduct of clinical research:

1. Standards
2. Protocol review
3. Biostatics support
4. Clinical informatics, data management and protocol tracking
5. Quality assurance and quality control
6. Human resources and physical plant
7. Training and education

The various NIH institutes will be implementing these standards over the next few years; therefore, you should be familiar with them. You can find the standards at **http://www.cc.nih.gov/ccc/clinicalresearch/standards.html**.

The NIH Federal Wide Assurance, FWA

Research institutions that receive U.S. government funds to conduct research involving people must abide by federal requirements. The NIH's HRPP has an FWA which is its written assurance to the Department of Health and Human Services (DHHS) that it will abide by these requirements including the ethical principles of the Belmont Report and the federal regulations for the protection of human subjects (45 CFR 46). The FWA requires that the NIH have policies and procedures in place for how it carries out its human subject protections activities.

Therefore, NIH's policies clarify the responsibilities of NIH IRP researchers who conduct, support or collaborate in research involving human subjects, NIH's Institutional Review Boards (IRBs) and the NIH's Office of Human Subjects Research (OHSR).

You do not need to know the details of NIH's FWA. However, as an NIH researcher you should be familiar with NIH's policies and procedures or know whom to call if you have questions. If you have questions about NIH's HRPP or its policies and procedures you may contact the IRB in your Institute or you may call OHSR at 301-402-3444.

The NIH Intramural Research Program (IRP)

IRP

A description of the NIH's HRPP and its policies and procedures of NIH's HRPP can be found at the following sites:

- **A general overview and description of NIH's HRPP:**
  The NIH Manual Chapter #3014 - The NIH Human Research Protection Program
  (see **http://www1.od.nih.gov/oma/manualchapters/intramural/3014/**)
- **CC policies related to the conduct of clinical research:**
  The Medical Administrative Series (MAS)
  Note: These documents are NIH accessible only
  (see **http://intranet.cc.nih.gov/mec/mas/index.shtml**)
- **OHSR Information Sheets:**on the Office of Human Subjects Research (OHSR) web site
  (see **http://ohsr.od.nih.gov**)

Other policies that might apply to your research include:

- **Radiation used for research purposes:**
  Radiation Safety Committee
  (see **http://www.nih.gov/od/ors/ds/rsb/rsc.html**)
- **Gene transfer/therapy and other biotechnology policies:**
  The NIH Office of Biotechnology Activities (OBA)
  (see **http://www4.od.nih.gov/oba**)

Before we discuss the roles and responsibilities of NIH's IRBs, we will review briefly the differences between the NIH's Office of Human Subjects Research (OHSR) and DHHS's Office for Human Research Protections (OHRP).

The NIH recognizes that sometimes it is not easy to understand if and how NIH IRP policies and procedures apply to your research activities. Therefore, in 1991, the NIH established its Office of Human Subjects Research (OHSR) to help you understand and comply with its policies and procedures.

OHSR works for the DDIR and exists to help YOU and other IRP researchers. It is a different office from DHHS's Office for Human Research Protections (OHRP). If you have questions about NIH policies and procedures related to the protection of human subjects you should contact your IRB chair or OHSR.

OHSR is located in Building 10, Room 1C116. The phone number is 301-402-3444 and its FAX number is 301-402-3443.

The activities of NIH's OHSR include the following:

- Supporting NIH's commitment to conduct innovative human subjects research consistent with well-established ethical principles and regulatory requirements
- Working with NIH's 14 IRBs to promote their mandate to protect human subjects
- Consulting with PIs and others upon request to help identify and resolve ethical and regulatory issues associated with the conduct of their human subjects research activities
- Serving as the IRP's main resource for information and education on the protection of human subjects, and
- Serving as the NIH IRP's liaison with the DHHS Office for Human Research Protection (OHRP)

OHSR maintains a web site at **http://ohsr.od.nih.gov** which includes much useful information including The Belmont Report, 45 CFR 46, OHSR Information Sheets.

On the other hand, the Office for Human Research Protections (OHRP) is an office in DHHS.

OHRP:

- Was formerly called the Office for Protection from Research Risks (OPRR)
- Was reorganized and moved from the NIH to DHHS
- Oversees the protection of human subjects involved in research conducted with DHHS funds throughout the U.S. and abroad

OHRP has a number of responsibilities, including approving assurances on behalf of the Secretary, HHS. Since 1998, OHRP has suspended or restricted the assurances of 12 major US research institutions. These actions were taken because OHRP determined that these institutions' procedures related to the protection of human subjects were insufficient.

Test Your Knowledge

To test your knowledge about Institutional Review Boards (IRBs), answer the following question:

What is the primary mandate of NIH's IRBs?

A. **To promote NIH research involving human subjects**
B. **To provide detailed, primary scientific review of research protocols**
C. **To protect the rights and safeguard the welfare of the research subjects**

Answer

What is the primary mandate of NIH's IRBs?

A. To promote NIH research involving human subjects
B. To provide detailed, primary scientific review of research protocols
C. **To protect the rights and safeguard the welfare of the research subjects**

The answer is **c**. The primary mandate of IRBs is to protect the rights and safeguard the welfare of the research subjects.

NIH Institutional Review Boards (IRBs)

What is the role of an IRB?

It is not the job of the IRB to promote your research.

It is the job of the IRB to review your protocol to insure that you design and conduct research according to agency and institution regulations and guidelines for protecting the rights and welfare of NIH human research subjects. It is through this process that investigators, institutions and IRB members are held publicly accountable. As a Principal Investigator you need to understand and appreciate the role of the IRB in your clinical research.

How many IRBs does the NIH have?

The NIH has 14 IRBs made up of more than 180 members. These IRBs oversee about 1300 active protocols in the Clinical Center and about 200 protocols for research collaborations in which human subjects are located at domestic and international non-NIH sites.

The following NIH ICs have IRBs: NCI (2 IRBs), NEI, NHLBI, NIAAA, NIAID, NICHD, NIDA, NIDDK/NIAMS, NIDCR, NIEHS, NIMH, NINDS/NIDCD/NIA, and NHGRI.

What is the Most Effective Way to Work with IRBs?

Although IRBs and PIs have different roles and responsibilities, they share a commitment to insure that research subjects are protected.

As a PI you will work most effectively with IRBs if you understand the information needed for IRB review and you provide the required information to the IRB in a clear, thoughtful way.

What are the IRB Protocol Review requirements?

Although NIH's 14 IRBs are given discretion in many aspects of their review, all are expected to meet minimal requirements when reviewing protocols.

45 CFR 46 and NIH policy provide minimal requirements for IRB review and approval of research. In order to approve your research protocol, the IRB must determine and document in its minutes that the protocol meets all of the following requirements:

- The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk
- Risks to subjects are reasonable in relation
- Risks to subjects are minimized
- Subject selection is equitable
- Informed consent is obtained from research subjects or their legally authorized representative
- Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence
- Subject privacy and confidentiality are maximized

Review the **NIH IRB review standards** in a new window.

As an NIH PI you are expected to understand the review standards and address each in your written protocol and in oral presentations to IRBs.

If you do, you will improve the likelihood that your protocols will receive IRB approval.

Below is the list of the **NIH IRB Review Standards** that will be discussed in more detail on the following pages:

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.*	NIH's leadership expects all research protocols to receive substantive scientific review *before* they are reviewed by an NIH IRB. NIH requires "that its IRBs will review only research which has been reviewed by the appropriate Institute or Center (IC) and found to be scientifically meritorious, well designed, and in keeping with ethical guidelines, program relevance, and public responsibility." Each NIH Institute and Center (IC) is expected to have a system for adequate scientific review of research protocols before they are sent to an NIH IRB for review. However, ICs are given wide discretion in how to accomplish this task. For example, some have pre–IRB scientific review committees, some send their protocols out for scientific review by outside (non-NIH) experts, and some have intramural experts evaluate protocols. Adequate pre–IRB scientific review is important because: • An IRB's main mandate is to protect the rights and safeguard the welfare of research subjects. Although NIH's IRBs have members with scientific expertise, they are not constituted to act as primary scientific review committees. • If a research protocol is poorly designed and not likely to obtain meaningful information, it is not ethically justifiable to expose subjects to any risk, discomfort or inconvenience. Therefore, IRBs deserve some assurance that the research they are asked to review has received prior, adequate review by scientific experts. IRBs should assure themselves that all new research protocols they review have received pre–IRB scientific review. However, for each protocol they review, IRBs are expected to determine and document in the minutes that: 1. The hypothesis is clear; 2. The study design is appropriate; and 3. The research will contribute to generalizable knowledge and that it is justifiable to expose subjects to risk, discomfort, or inconvenience. If an IRB determines that a protocol is not scientifically sound — the hypothesis is not clear, the study is poorly designed (i.e., statistically not valid) — its courses of action include: 1. It may attempt to resolve the major scientific issues, keeping in mind that its main task is to protect the rights and welfare of human research subjects and that it is not constituted to be a scientific review committee. If the IRB chooses this approach, its minutes will contain a number of stipulations (required changes) to which the PI must respond adequately before the protocol is considered for re-review. 2. It may table the protocol and refer it back to the PI. 3. It may choose to ask the pre–IRB scientific review group to re–review the protocol or it may request that an ad hoc consultant(s) review the protocol and provide guidance in writing and/or by attending an IRB meeting to discuss it. 4. It may disapprove the research protocol. However, the best situation is for each IC to have high quality pre–IRB scientific review of protocols so that when an NIH IRB reviews a protocol, it can give most of its attention to the protection of the subjects rather than the details of the scientific design. Regardless of which of these approaches it takes, before approving a research protocol, the IRB must assure itself, and document in its minutes, that the proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.

NIH IRB Review Standard

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.*	As discussed in The Belmont Report, the ethical principle of beneficence requires researchers, and others, to protect research subjects by maximizing possible benefits and minimizing possible harms of research participation. This principle requires that researchers and IRBs have adequate information concerning, and give careful consideration to, the risks and benefits of research participation. To review the Belmont Report, go to OHSR's web site at **http://ohsr.od.nih.gov.** In addressing this review standard, the NIH IRB, in consultation with the Principal Investigator (PI) of the protocol being reviewed, is responsible for determining: • The risk(s), discomfort(s) and inconvenience(s) to subjects • The level of risk to research subjects, and • Whether or not there is prospect of direct benefit to individual research subjects Therefore, NIH PIs are required to provide a section in their research protocols entitled "Human Subjects Protections" which includes an evaluation of research–related benefits (to the subjects or to others) and the research–related risks, discomforts and inconveniences. NIH IRBs ought not approve research protocols which do not contain this section. However, keep in mind two things: 1. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of procedures or interventions subjects would receive even if not participating in research). **Example:** A research protocol proposes to give persons with cancer a standard FDA-approved chemotherapy. The research consists of performing positron emission tomography scans (PET scans) before, and at several time intervals after, completion of the chemotherapy. The IRB's evaluation of risks, discomforts and inconveniences should focus on those of the research (the PET scans) rather than of the chemotherapy. 2. The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effect of research on public policy) as among those research related risks that fall within the purview of its responsibility. **Example:** • Information gained from research about associative memory may enable advertising companies to develop new techniques, such as subliminal advertising, for encouraging arguably harmful consumer behaviors (e.g., smoking) • Research on associations between race, gender and intelligence may have profound effects on public policy Let's evaluate further the IRB's responsibility for determining level of risk to research subjects and review what guidance is provided in the regulations (45 CFR 46). Minimal risk "means that the *probability* and *magnitude* of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or the performance of routine physical, psychological examinations or tests" (45 CFR 46.102{i}). A definition of "minimal risk" is provided because some research activities determined to be of minimal risk are eligible for IRB review through expedited review procedures. This means that the IRB Chair, (and/or other IRB members designated by the Chair) may approve the research on behalf of the IRB. If you would like to review a list of procedures that are eligible for review under expedited review procedures, go to OHSR's web site at **http://ohsr.od.nih.gov.** and click on NIH Multiple Project Assurance. The IRB is responsible for determining the level of risk to research subjects For each new protocol they review through their regular review procedures (non–expedited

procedures), NIH IRBs are required to determine and document in their minutes which of the following applies:

1. The research involves no more than minimal risk to subjects,
2. The research involves more than minimal risk to subjects and the risks represent a minor increase over minimal risk, or
3. The research involves more than minimal risk to subjects and risks represent more than a minor increase over minimal risk.

Federal regulations define only “minimal risk” and thereforewhat constitutes “minor increase over minimal risk” and “greater than minimal risk” are for the IRB to judge on a protocol–by–protocol basis.

Although Federal regulations require IRBs to categorize research activities according to level of risk only when children are research subjects, it is an NIH standard that its IRBs categorize all research protocols into one of these risk levels and document their decisions in the minutes.

Research–related risks refer to the probability of harm to subjects and may vary in magnitude. Ambiguous terms such as “small or low risk” and “high risk” are best avoided by IRBs.

When determining the magnitude of risks presented by research procedures or interventions — whether risks are minimal, a minor, or more than a minor increase above minimal risk — the IRB may want to consider at least four approaches:

1. A common–sense estimation of risk;
2. An estimation based upon investigators’ or others’ experience with similar interventions or procedures;
3. Any statistical information (or other information in the medical literature) that is available regarding such interventions or procedures, and
4. The situation of the proposed research subjects; for example, are potential subjects ill, healthy, young, institutionalized, etc.

The IRB is responsible for determining the level of risk to research subjects (continued)

In determining risks and potential harms to research subjects, the IRB needs to consider not only physical harms but also psychological, social and economic harms and other aspects of the research study which may weigh in a negative fashion in the research participant's decision making process.

Example:

An IRB is evaluating research on genetic testing for a heritable neurological disease which requires obtaining 5cc of blood. The risks of taking the blood are minimum; however, the psychological and social risks to the person may be high.

Now let’s briefly consider what is meant by research–related “benefits.”

“Benefit” is used in the research context to refer to something of positive value related to health or welfare.

Benefits of research fall into two major categories:

- Direct benefits to subjects and
- Benefits to others (and to society by the advancement of knowledge through research)

IRB is responsible for determining if there is prospect of direct benefit to individual research subjects

In some research studies, the subjects are undergoing examination, diagnosis or treatment for an illness or an abnormal condition. Therefore their research participation may hold out the prospect of direct benefit to them by ameliorating their condition or providing a better understanding of their disorder.

On the other hand, patients and healthy individuals may agree to participate in research that either is not related to any illness they might have or that is related to their condition(s) but not designed to provide any diagnostic or therapeutic benefit to them. This type of research is not intended to benefit the subjects directly but nonetheless may benefit others in the future with the same disease as well as society as a whole. These benefits take the form of increased knowledge, improved safety, technological advances and better health for persons in the future.

Monetary payment (or other material compensation such as coupons, etc.) for research participation should not be considered a “benefit” to subjects but rather remuneration for research–related inconveniences and discomforts.

When a research protocol calls for monetary payments or other compensations, IRBs are expected to review and approve the proposed amount, timing of payments, etc. This is to assure that the remuneration is not so high as to induce potential subjects to take on risks or discomforts which

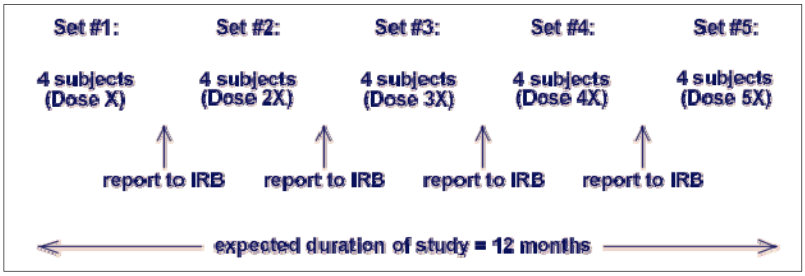
	they would not accept without payment. The amount of monetary payment or other compensation should be disclosed in the consent document. For each protocol it reviews, an NIH IRB is expected to discuss and document in its minutes whether: 1. The research involves the prospect of direct benefit to individual subjects, OR 2. The research involves no prospect of direct benefit to individual subjects, but is likely to contribute to generalizable knowledge. When reviewing a research protocol, not only is the IRB responsible for identifying research–related risks and benefits, but also for determining if the risks are reasonable in relation to anticipated benefits. An IRB's risk/benefit assessments are judgments made on a protocol–by–protocol basis and begin with its determination of whether the research design will yield useful data (see NIH IRB review standard #1, above). While good scientific design may not itself eradicate or reduce risks to subjects, poor or faulty research design indicates that the risks are not reasonable in relation to the benefits. Risks are reasonable in relation to anticipated benefits Risk/benefit assessments take into account a number of other factors including prevailing community standards, subjective determinations of, and currently available information about, risks and benefits, as well as the degree of confidence about this information. For example, information drawn from animal research may be highly suggestive of the risks and benefits to be expected in humans but it may not be conclusive (because human responses may differ from those of animals). Similarly, absence of information concerning risks does not necessarily mean that there are no risks. Also, the relation of risks and anticipated benefits must take into account the proposed subjects of the research (children, terminally ill) and other considerations which may influence subjects' ideas about research–related risks and benefits. Example: • Terminally ill individuals may value proximity to family and may therefore view as undesirable participation in research which requires hospitalizations • An elderly person may consider hair loss or a scar as insignificant, whereas a teenager could well be concerned about them Risk/benefit assessments will be influenced strongly by whether or not the research holds out the prospect of direct benefit to individual subjects. If research subjects stand to benefit directly from participation in the research (because they are receiving treatment or diagnostic procedures), higher risks and discomforts may be justifiable. On the other hand, in research where no direct benefits to subjects are anticipated, the IRB must evaluate whether the risks to subjects presented by procedures/interventions solely to obtain generalizable knowledge are ethically acceptable.

NIH IRB Review Standard

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *3. Risks to subjects are minimized*	This IRB Review Standard is closely related to and most likely will be discussed along with IRB Review Standards #1 and #2. Even when research risks are justifiable and unavoidable, often they can be reduced or managed effectively. Precautions, safeguards, and/or alternatives can be incorporated into the protocol to reduce the probability of harm or reduce its severity. If research subjects stand to benefit directly from participation in the research (because they are receiving treatment or diagnostic procedures), higher risks and discomforts may be justifiable. IRBs are responsible for assuring that risks are minimized to the extent possible. In order to minimize risks, IRBs may want to ask: 1. Are adequate safeguards incorporated into the protocol? 2. Is the monitoring of data proposed in the research protocol appropriate? 3. Are the investigators competent in the area(s) being studied? 4. Do investigators serve dual roles (e.g., treating physician, teacher, employer) in addition to researcher that may complicate their interactions with the subjects? **Are adequate safeguards incorporated into the protocol?** Examples of safeguards include appropriate clinical and laboratory monitoring of subjects enrolled in the protocol, establishment of end and stopping points, proper storage of data to protect confidentiality, the presence of trained personnel to respond to emergencies, and written procedures for identification and reporting of adverse events (AEs) to the IRB. At a minimum, all NIH protocols must define an "adverse event" and IRBs are expected to assure that the PI's plans for identifying and grading AEs and the time-frame for reporting them to the IRB are appropriate for the protocol under consideration. Also, it may be necessary to exclude individuals or classes of subjects (e.g., pregnant women, persons with diabetes or hypertension) whose sensitivity to a drug or procedure may increase their risks. Therefore, in order to minimize risks to subjects the IRB should always evaluate carefully the inclusion (eligibility) and exclusion criteria for the protocol. Blinded, randomized studies require special attention. Random assignment and blinding are methods used in clinical trials to reduce bias and enhance study validity. However, both require justification because when randomized and blinded, subjects neither have a say in their choice of experimental treatment nor do they (or the researcher(s)) have information about what experimental treatment(s) they are receiving. In order to balance the need for scientific objectivity with the concern for subject safety, the protocol should discuss conditions in which the blind may be broken to treat adverse events. Discussion might include identification of where the code is located, the circumstances in which it may be broken, who will break it, how information will be handled (will the investigator, subject, IRB, treating physician be informed?), and how breaking of the blind will influence analysis of data. More about these issues can be found in OHSR Information Sheet #13, "Issues Regarding Blinded, Randomized Studies in the Intramural Research Program" which is available on OHSR's Web site. **Is the monitoring of data proposed in the research protocol appropriate?** The Principal Investigator (PI) of the protocol is responsible for monitoring research data and the clinical status of the subjects. Also, federal regulations require that research protocols receive continuing review by an IRB at least annually. However, an IRB may determine that more frequent monitoring of research data is necessary in some types of research. We will discuss continuing review further in the next Lesson. **Example:** Researchers in the National Cancer Institute (NCI) receive IRB approval to conduct a Phase

1 clinical trial which is scheduled to take 12 months to complete. 20 subjects (five sets each made up of four subjects) will receive increasingly higher doses of a new chemotherapeutic agent. This agent has never been given to humans before and some of the toxicities seen in animals concern the IRB. Therefore, the IRB decides to require the PI to provide updates to it after all four persons in each set have received the agent, before the next highest dose is administered.



In certain types of clinical trials such as double–blinded multi–center trials, monitoring by a single IRB may not be practicable and special provisions may need to be made for monitoring incoming data from all the sites at set intervals.

In these situations, the IRB or the sponsor of the research (the NIH, a pharmaceutical company, etc.) may choose to establish a data and safety monitoring board (DSMB) to review the incoming data at stated intervals. This is in order to ensure the safety of subjects, to ensure that no group or subgroup is given a less effective treatment, and/or to ensure that the trial does not continue after reliable results have been obtained.

Are the investigators competent in the area(s) being studied?

The knowledge and experience that researchers require to conduct a study depends on the type of research.

For example, qualifications and experience required for researchers to administer a questionnaire eliciting non-sensitive information from adult subjects are different from those required when conducting research in emergency circumstances. In the latter instance, potential subjects may be cognitively impaired. Therefore researchers must be familiar not only with procedures for determining potential subjects' mental capacities to provide consent but also for identifying a "legally authorized representative" to provide consent for incapable subjects.

IRBs are responsible for assuring that the researchers conducting the protocol have the necessary qualifications, skills, and knowledge of NIH policies related to the research.

Do investigators serve dual roles (e.g., treating physician, teacher, employer), in addition to researcher, that may complicate their interactions with the subjects?

IRBs should pay particular attention to researchers' potential and/or real conflicts of interest.

Example:

The IRB will pay particular attention to:

- Financial conflicts; for example, the NIH or its researchers receive royalties for products or patents
- Conflicts experienced when researchers serve in dual roles; for example, when the researcher is also the subject/patient's physician or when the researcher is the subject's teacher or employer

Although physicians and clinical researchers have similar long term goals — to alleviate pain and suffering and to prevent and cure human diseases — their roles are different. As physicians or other health care professionals, they are dedicated to promoting the welfare of individual patients. As researchers, they seek knowledge applicable to persons other than their individual patients. The second goal may conflict with the first.

IRBs have one paramount goal — to protect the rights and safeguard the welfare of the human subjects.

Therefore, IRBs need to be particularly vigilant in identifying and minimizing potential and real conflicts of interest when physicians are also researchers.

The IRB may want to know more about the relationship of the researcher and patient/subject. If an investigator also serves as the patient's physician, the patient may feel obliged to participate in research out of a desire to please or fear that failure to do so will result in hostility or abandonment. In this case, the IRB may not allow the research or may require an individual not involved in the research to take over the patient's primary medical care during participation in

	research. Because the CC is a research facility this problem is minimized. Generally, individuals are referred to the CC by their personal physicians. Therefore, when they are no longer participating in CC research they return to the care of their physicians. If you would like to read more about some ethical considerations involved when a physician is also a researcher, please call OHSR at 301-402-3444.

NIH IRB Review Standard

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *4. Subject selection is equitable*	The requirement for the equitable selection of subjects is based on the ethical principle of justice, which requires fair distribution of both the burdens and benefits of research. In the past the burdens of research in the United states often fell largely upon poor patients in public hospital wards and chronic care institutions, while the benefits flowed primarily to private patients. In the mid-1970s there was a national outcry against some researchers conducting studies involving only poor, elderly, or institutionalized persons. In large part, the Belmont Report and the implementation of federal regulations for the protection of human subjects were a response to these and other research studies which were thought to be unfair. IRBs are required to give careful attention to subject selection to determine whether some classes of subjects (e.g., welfare patients, racial and ethnic minorities, or persons confined to institutions) are being systematically selected because of their easy availability, their compromised position or manipulability, rather than for reasons directly related to the problem being studied. **Example:** In the United States during the 1950s through the mid-1970s many chemotherapeutic agents for cancer (and other diseases/disorders) were tested initially in healthy prisoners. In fact, some pharmaceutical companies had research buildings located on or near prisons to facilitate their research activities. Often the goals of the research were totally unrelated to prisoners' health needs. They were used merely because their incarceration simplified recruitment, retention and follow up. A researcher proposes to conduct a study on the effects of biofeedback and acupuncture in the management of migraine headaches. He plans to exclude pregnant women for reasons that are not clear to the IRB. However, migraine headaches are a significant problem for many pregnant women and most of the IRB members think they should be included in the study. Therefore, the IRB asks for more information about why the researcher proposes to exclude them. Today, special provisions are in place for research involving prisoners, pregnant women and children. If you are interested in learning more, please see 45 CFR 46, Subparts B, C, D. Defining the appropriate group of subjects to be studied in a research protocol involves a variety of considerations — requirements of scientific design, considerations of practicability and fairness, potential subjects' susceptibility to risk, and the likelihood of direct benefits. When reviewing a protocol for the first time (initial review), NIH IRBs are expected to make a determination that the selection of subjects is scientifically and ethically appropriate. They are assisted in this determination by NIH PIs who, at a minimum, are required to provide in their protocols: 1. The rationale for the subject selection based on a review of the gender/ethnic/race categories of persons at risk for the disease or condition being studied in the protocol; 2. Strategies/procedures for recruitment (including advertising, if applicable), and 3. The rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, cognitively impaired individuals, prisoners or other institutionalized persons or others who are likely to be vulnerable to coercion or undue influence (discussed further in Review Standard #6). NIH IRBs should not accept for initial review protocols which do not contain this information. Let's briefly discuss each of these requirements. **NIH PIs are required to provide in their protocols the rationale for the subject selection based on a review of the gender/ethnic/race categories of persons at risk for the disease or condition being studied in the protocol.** When the NIH funds research it expects the findings to be of benefit to all persons at risk for the disease, disorder or condition under study. Therefore, adequate representation of women and

	minorities is particularly important in studies of diseases, disorders and conditions that affect them. If a proposed protocol includes a study population in which women and minorities are not appropriately represented, the investigator must provide a clear, compelling reason for their exclusion or inadequate representation. If you want to learn more, go to the OHSR Web site and read **OHSR Information Sheet #11**, Inclusion of Women and Minorities in Study Populations (Guidance for IRBs and Principal Investigators). **NIH PIs are required to provide in their protocols strategies/procedures for recruitment, including advertising, if applicable.** This requirement is to promote inclusion of a broad cross-section of research subjects and to promote fair recruitment practices. For example, the IRB may want to know if notices will be placed on bulletin boards in graduate and/or undergraduate schools, in shelters for the homeless, or in medical clinics for persons who are indigent. If a researcher's sole method of recruitment is to write letters to private physicians, an unintended effect may be exclusion of persons without private physicians; therefore, additional recruitment procedures may be warranted. **NIH PIs are required to provide in their protocols strategies/procedures for recruitment, including advertising, if applicable.** Advertisements are considered an extension of the informal consent process. Therefore, NIH IRBs are expected to review all advertisements and recruitment notices associated with protocols they approve. Some institutions have guidelines that prohibit professors from soliciting their students as subjects and supervisors from including their employees in research. The NIH has a policy that guides the involvement of its employees in NIH research. To receive a copy of this policy call OHSR at 301-402-3444. **3. Explain the rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, cognitively impaired individuals, prisoners or other institutionalized persons or others who are likely to be vulnerable to coercion or undue influence.** *(see Review Standard #6)* We will discuss this in detail in the next section. However, when researchers request permission to study persons who are particularly vulnerable to coercion or undue influence, IRBs should determine if these subjects are being systematically selected for reasons directly related to the problem(s) being studied and not, for example, because of their easy availability, their compromised position or manipulability. The principle of justice not only underlies ethical considerations about who ought to be the subject of a research protocol but also the expectation that persons who accept the risks or burdens of being research subjects should share in its benefits whenever possible. For example, those who have participated as research subjects should have the first opportunity to receive a therapy if the research demonstrates it to be safe and effective. For example, subjects of clinical trials who were either in a control group or recipients of a therapy that proved not to be superior should be offered the treatment that the trial demonstrated to be preferable.

NIH IRB Review Standard

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *5. Informed consent is obtained from research subjects or their legally authorized representative(s).*	The principle of respect for persons is based on the ethical conviction that individuals should be treated as autonomous agents. An autonomous person is capable of deliberating about and acting upon personal choices. To respect autonomy is to give weight to his/her considered choices. Therefore, providing the opportunity for informed consent to research participation is one way to demonstrate respect for research subjects. We will discuss briefly a few issues related to subjects' informed consent. IRBs' considerations of informed consent generally include the following: 1. Adequacy of the content and clarity of the written consent document; 2. The process of informed decision making; 3. Documentation of informed consent, and 4. Exceptions: Waiver or alteration of some or all of the requirements for written informed consent. **Adequacy of the content and clarity of the written consent document.** Except in specific circumstances approved by an IRB (which we will discuss later), subjects' written informed consent is necessary. Therefore, IRBs give much attention to written informed consent documents to assure that they contain the required information in a manner that promotes understanding by prospective subjects. Federal regulations give requirements for minimal research–related information which must be disclosed to prospective subjects. Click the Next button to review the general requirements for informed consent. The following information shall be provided to each subject: 1. A statement that the study involves research, and an explanation of the purposes of the research; the expected duration of the subject's participation; a description of procedures to be followed, and identification of any procedures which are experimental; 2. A description of any foreseeable risks or discomforts to the subject; 3. A description of any benefits to subjects or to others which may reasonably be expected from the research; 4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. 5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained; 6. For research involving greater than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of and where further information may be obtained; 7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subjects; and 8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. When appropriate, one or more of the following elements of information shall also be provided to each subject: 1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) which are currently unforeseeable; 2. Anticipated circumstances in which the subject's participation may be terminated by the investigator without regard to the subject's consent;

3. Any additional costs to the subject that may result from participation in research;
4. The consequences of the subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
6. The approximate number of subjects involved in the study.

The NIH provides to IRP researchers standard language that covers most but not all the required elements of consent. This standard language is provided on the first and last pages of the standard NIH CC consent form. To review this standard language, click the Next button.

Standard written consent document language.

Introduction

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

- Taking part in NIH research is entirely voluntary.
- You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.
- You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

(Information related to the specific protocol begins here and continues on subsequent pages, as necessary.)

Standard written consent document language.

Other Pertinent Information

1. **Confidentiality.**
   When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.
   The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.
2. **Policy Regarding Research-Related Injuries.**
   The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.
3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.
4. **Problems or Questions.**
   If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Building , Room , Telephone: . Other researchers you may call are: You may also call the Clinical Center Patient Representative at 301-496-2626.
5. **Consent Document.**

Please keep a copy of this document in case you want to read it again.

Although the NIH requires its standard language to be incorporated into the consent document, a researcher or IRB may decide that the standard language is not adequate and that more must be said in the body of the consent document.

Example:

An NIH IRB reviews a research protocol involving women which collects information about the genetic basis of breast cancer. The researcher and IRB agree that the NIH's standard language on confidentiality is not sufficient for this protocol and that the consent document should include a specific discussion of confidentiality concerning the genetic information obtained in the study.

When you review a research consent document, ask yourself at least the following four questions:

1. Is it written at a reading level understandable to research subjects?
2. Does it contain the general requirements for informed consent and are they presented in a clear, easy-to-understand way?
3. Can the document be shortened without compromising other requirements?
4. Is the document formatted well? Is the text broken into short sections with headings that make the document easier to read?

Even though much IRB attention may focus on the written informed consent document, informed consent is a process in which the consent document is only one important aspect.

Other influences on the process include:

- The skill and experience of the investigator(s) obtaining consent (for example, relating well to subjects, getting complicated points across, listening to and answering subjects' questions)
- Subjects' level of education, state of physical and emotional health, primary language and many other personal factors including religion, cultural background, financial considerations, attitudes and beliefs about health
- Educational activities surrounding the process, including discussions with nurses and others, and information gleaned by prospective subjects from other sources including the World Wide Web, and
- The circumstances and environment in which the process takes place

Depending on the protocol, the IRB may want specific details about the informed consent process.

Example:

Researchers propose to study people with chest pain coming for care to a local hospital emergency room. Because these prospective subjects will be acutely ill and making decisions about research participation in an emergency environment, the IRB requests information about who will be obtaining informed consent, where it will take place and what procedures, if any, the researchers plan to implement to promote informed decision making.

In general when reviewing protocols, the IRB should ask who will be obtaining informed consent from prospective subjects. If the Principal Investigator (PI) is not obtaining it, the IRB will want to know who he/she will delegate to obtain consent and receive assurance from the PI that the designee(s) are qualified to take on this important responsibility.

Regardless of who obtains consent, the PI remains responsible for all aspects of the study. Therefore he/she must not delegate this responsibility lightly.

An IRB may designate IRB member(s) or others to observe the process of informed consent or discuss the study with prospective subjects after they agree to participate. Although these options are not exercised often by NIH IRBs, they can be important safeguards in some circumstances.

Example:

Researchers at the NIH's Clinical Center conducted the first human gene therapy study. The IRB required that all subjects who provided informed consent discuss the study with the CC patient representative in order to assure that they understood the investigational nature of the research and had an opportunity to discuss the study with someone who was not a member of the research team.

Documentation of informed consent

Although written informed consent is required for most research participation, there are exceptions. Your IRB Chair can provide information on these exceptions. These exceptions can be viewed on the next page.

Example:

- Researchers want to obtain blood samples for research purposes and propose that the Clinical Center phlebotomists draw an extra 5 cc of blood from 20 patients having blood drawn for other purposes. The researchers consider taking the extra small amount of blood to be minimal risk to persons already undergoing phlebotomy and they ask the IRB for a waiver from the requirement for informed consent. The IRB disapproves this request because it believes that is practicable for the researchers to obtain consent for the research procedure.
- Researchers have 1000 frozen blood samples previously collected from and linked to persons with cancer. The researchers now want to use the stored samples to conduct a preliminary test for a new tumor marker. The results will have no impact on the clinical care of these patients. The researchers ask the IRB for a waiver from the requirement to obtain informed consent for this research use of the samples because they say that it is not possible to locate many of these persons, most of whom receive medical care at institutions around the country, and they believe the risk to subjects is minimal. The IRB grants their request.

Waiving informed consent

An IRB may waive or alter some or all of the requirements for written informed consent if the IRB determines that the research meets the following criteria (see 45 CFR 46.116(d)):

- The research involves no more than minimal risk to subjects
- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- The research could not practicably be carried out without the waiver or alteration, and
- Whenever appropriate, the subjects will be provided with additional pertinent information

The definition of "minimal risk" is:

Minimal risk means "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or the performance of routine physical, psychological examinations or tests".
(45 CFR 46.102{i})

When a prospective adult subject cannot provide consent, because of severe illness or other reasons, the consent of the subject's "legally authorized representative" is required.

Legally authorized representative (LAR) means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to his/her participation in research (45 CFR 46.102(c)).

This definition is somewhat problematic because there is no federal regulation that directs who may be an LAR for research purposes. Also, although most states have statutes directing who can make health care decisions on behalf of another person, most, including Maryland, are silent on research decision making. Therefore, the NIH has implemented policies that help researchers identify who may act as an LAR in some types of research. We will discuss this topic a little more in the next review standard.

In any event, if prospective subjects will not themselves provide informed consent, the IRB should ask the investigator who will provide consent and whether that person can be considered an LAR.

NIH IRB Review Standard

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.*	Informed consent is one way researchers demonstrate respect for the autonomy of prospective research subjects. However prospective research subjects who are incapable of self-determination also are entitled to protection. Generally the capacity for self-determination matures during an individual's life, however some persons never develop it (e.g., severe mental retardation) and some lose it because of illness, mental disability or circumstances that severely restrict liberty (imprisonment). Protecting human subjects with diminished autonomy is addressed broadly in HHS regulations: "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects." *(45 CFR 46.111(d))* Therefore, 45 CFR 46 expects IRBs to determine whether prospective subjects are vulnerable to coercion or undue influence AND, if appropriate, to include additional safeguards in the protocol for them. However, little practical guidance on additional protections is provided, except when the subjects of research are pregnant woman and fetuses *(45 CFR 46, Subpart B)*, prisoners *(45 CFR 46, Subpart C)*, or children *(45 CFR 46, Subpart D)*. Research involving pregnant woman, fetuses or prisoners will not be discussed further, although you may review and print out Subparts B and C from the OHSR web site. We will discuss briefly research involving "vulnerable" subjects and requirements for conducting research involving children *(45 CFR 46, Subpart D)*. Vulnerable research subjects are persons who are relatively or absolutely incapable of protecting their own interests. "They have insufficient power, prowess, intelligence, resources, strength or other needed attributes to protect their own interests through negotiations for informed consent." *(Robert J. Levine, "Ethics and Regulation of Clinical Research.", Yale University Press, 1988, P.72)* In many instances, the determination of whether prospective subjects are vulnerable to coercion or undue influence is not difficult. Clearly, persons who cannot provide their own informed consent — for example, comatose persons, persons with severe head injury or massive trauma — are vulnerable subjects and deserve additional protection when participating in a research study. In these cases, at a minimum, an IRB must determine who may provide informed consent on subjects' behalf for participation in research. The determination of whether or not subjects are vulnerable to coercion or undue influence is a judgment made on a protocol–by–protocol basis by the IRB in consultation with the PI. Here are a few examples of prospective subjects who are, or may be, vulnerable because of their limitations in providing informed consent or because they may be susceptible to coercion or undue influence. Susceptible to coercion or undue influence Limitations to informed consent comatose persons -critically ill persons -mentally retarded persons -persons with dementias/some psychiatric diseases -individuals who are chronically institutionalized -non-English speaking people -children -the educationally/economically deprived

-prisoners

-seriously/terminally ill people

-paid healthy volunteers

Often, whether additional protections are necessary, and what they consist of, are also matters of IRB judgment.

Example:

A researcher submits to the IRB a protocol designed to study the effects of the first administration to humans of an investigational drug for AIDS. He plans to recruit prospective research subjects from an inner city medical clinic. The clinic is the only source of medical care available to these patients. All of them are poor, many are homeless, and over half do not speak English. The research requires a one month stay in the clinical research unit and the researcher plans to pay participants. After much discussion, the IRB tables the protocol because it is concerned that the prospective subjects, who have limited options for their medical care, may fail to appreciate fully the highly investigational nature of the research. Also, it is concerned about the lack of detail provided concerning the process by which informed consent will be obtained from non-English speaking and illiterate subjects. The IRB asks an ad hoc consultant, who has expertise in delivering medical care in this type of inner city, clinic environment, to attend the next meeting and provide guidance during its review. It also requests that the person obtaining consent from subjects who do not speak English accompany the PI to the next IRB meeting.

Example:

A researcher wants to conduct a study that requires obtaining a biopsy sample of nasal mucosa from healthy people without a history of allergies. This is the advertisement he plans to use to recruit prospective participants:

Participate in a research study and get a free nose job!!!

Do you think you have an ugly nose? Do you want to get a nose job (cosmetic rhinoplasty) but you can't afford the $2,500 bill? If you are a healthy person between the ages of 25—55 years and have no history of hay fever, this research study may be the solution to your problem. We are studying seasonal allergies (hay fever) and need healthy people to participate. Come and discuss with us what you don't like about your nose and whether we can surgically correct it. Also, we will discuss the research study with you. If you agree to participate, the research consists of allowing us to remove a small sample of the inside lining of your nose (biopsy). This research will be immediately followed by a free cosmetic rhinoplasty aimed at correcting your problem (this is a standard procedure and not part of the research). Participation in this research study will save you $2,500, which is the general rate in this area for a cosmetic rhinoplasty (nose job).

For more details call Kandi Cane at XXXXXX.

The IRB asks the PI if he believes the remuneration offered for participation in this study — a free rhinoplasty worth $2,500 — may be an undue coercion to participate in the research.

The NIH gives its IRBs wide discretion when making these decisions. However, NIH IRBs reviewing, and IRP researchers conducting, protocols involving cognitively impaired subjects at the CC or subjects seen in the emergency room at the Suburban Hospital, are guided by specific NIH policies concerning additional protections for these prospective subjects.

We will discuss these two policies briefly.

CC policy (MAS 87–4) on "Consent Process in Research Involving Impaired Human Subjects"

The Clinical Center (CC) Medical Administrative Series (MAS) 87–4 "Consent Process in Research Involving Impaired Human Subjects" sets forth additional protections for adult subjects who are, or are likely to become, cognitively impaired during their participation in research at the CC. This policy is applicable most often when research at the CC involves persons with dementia (such as Alzheimer's disease) and other illnesses that cause intellectual impairments.

The policy enumerates eight research situations in which additional protections for cognitively impaired subjects must be considered by an NIH IRB. These take into account the assumption in 45 CFR 46 that protection should be proportionate to the risk involved, with the least protection required when the research involves no more than minimal risk. Therefore, the most stringent protections are in place for subjects who are too impaired to provide their own informed consent and whose participation in research offers them no prospect of direct benefit.

If your IRB reviews a protocol which requires the use of this CC policy, your NIH IRB Chair will provide you with more information about it. Also, You may contact OHSR (301–402–3444) for a copy of the policy.

Example:

A CC researcher proposes to perform two brain Positron Emission Tomography (PET) scans and two lumbar punctures (spinal taps) within a six month period on persons with Alzheimer's Disease (AD). Each PET scan requires placement of an arterial line. Neither the PET scans nor the lumbar punctures will benefit subjects directly but researchers will learn about brain metabolism in AD. The researchers propose to include some subjects who have severe intellectual impairments. The IRB determines that this research is greater than minimal risk without prospect of direct benefit to individual subjects.

The IRB reviews the requirements of MAS 87–4. After much discussion, it decides that subjects may participate only if they can give their own consent or if they are intellectually capable of appointing a Durable Power of Attorney (DPA) for research decision–making. Also, each time a new subject is enrolled in the protocol, consultation with the CC Department of Clinical Bioethics is required. The IRB disallows involvement of subjects who are too impaired to consent or to appoint a DPA because in these cases, it believes that it is not ethically permissible to expose severely cognitively impaired subjects to the risks of this research when participation offers them no prospect of direct benefit.

Research conducted in the Suburban Hospital Emergency Department

The NIH's CC does not have an emergency room and until recently, IRP researchers were limited in their ability to study serious, acute illnesses such as heart attack, stroke, head injury and other emergency medical and surgical conditions.

Therefore, in August, 1997 an agreement was reached between the NIH and Suburban Hospital in Bethesda, Maryland to allow IRP researchers to conduct research in the Emergency Department at Suburban Hospital.

However, in emergency circumstances, a potential subject may be intellectually, emotionally or otherwise unable to provide informed consent. For example, even when a person is intellectually capable, acute illness and the environment of the emergency room can present serious time constraints and other barriers to informed decision making, both for medical care and research participation.

Therefore, the challenge to the investigator is to conduct important research in an emergency setting consistent with ethical guidelines and legal requirements.

The CC/Suburban Hospital guidelines provide information to IRBs and researchers concerning (1) who may act as a legally authorized representative for making decisions about participation in NIH-IRP protocols conducted in the Emergency Room (ER) at Suburban Hospital, and (2) additional safeguards for research subjects who present to the Suburban Hospital ER.

Your IRB Chair will provide more information on these guidelines if the IRB reviews a protocol in which research is conducted in the Suburban ER.

Example:

A CC researcher submits for IRB review a protocol to study the usefulness of standard brain magnetic resonance imaging (MRI) in understanding the progression of strokes. Persons with acute strokes will be evaluated in the Suburban Hospital Emergency Department where they will receive a standard neurological examination, have blood taken for clinical and research purposes, and receive a standard brain MRI to rule out other possible causes of their neurological deficit. The research consists of performance of a standard brain MRI (lasting about 30 minutes) daily for one week, then twice weekly for 3 weeks then weekly for 2 months. There is no prospect of direct benefit to individual subjects.

The IRB believes the medical risk to subjects is minimal but it is concerned about discomforts and inconveniences to these ill persons (they must remain very still during the large number of MRIs which are performed solely for research purposes). Also, the

researcher proposes to enroll subjects with strokes in their left brain hemisphere. Therefore, some subjects may have serious language problems which will limit their ability to communicate with the research staff.

The IRB determines that the written protocol does not contain the minimal requirements as set forth in the CC/Suburban Hospital guidelines. Therefore, it tables the protocol and sends it back to the PI to be re-written to include minimal requirements.

Children as research subjects

We will discuss briefly requirements for conducting research involving children.

On one hand, because of their physical and emotional immaturity and their dependent legal status, children are considered vulnerable research subjects. On the other hand, it is important for researchers to involve children in research in order to learn how to prevent childhood diseases and develop effective treatments for them.

Maintaining this balance — between protecting children and promoting their inclusion in important research — is achieved by IRBs and researchers taking into account:

- NIH guidelines for the inclusion of children in research and
- Federal regulatory requirements of 45 CFR 46 Subpart D (the latter are incorporated into CC policy MAS 92–5)

When reviewing research involving children, NIH IRBs are required to discuss and document in the minutes into which of four risk/benefit categories the research protocol falls. Each of the four categories incorporates protections for the child subjects.

The four allowable categories of research are:

1. Research not involving more than minimal risk;
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to individual child subjects;
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition, and
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

The most frequent types of research involving children conducted by IRP researchers fall into the first two categories (no more than minimal risk, or research involving greater than minimal risk but with prospect of direct benefit).

If you review research involving children, your IRB chair will discuss the additional protections required.

Example:

A research protocol studies children with bone cancer that has spread to involve the central nervous system (CNS). The protocol studies the ability of an investigational drug to treat the bone cancer and diminish its spread to the CNS. The IRB believes the protocol is well designed and meets all IRB review standards. However, several members of the IRB raise questions about the researcher's request to perform three additional lumbar punctures (LPs) solely for research purposes. He says the additional LPs will allow him to obtain large amounts of spinal fluid for

In order to minimize risks to the children, the investigator plans to perform research-related LPs only on children 12 years and older. Also he includes a written assent document for the research-related lumbar punctures.

The IRB determines that the drug administration part of the protocol represents category 2 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual child subjects). However, it believes that the additional LPs represent category 3 (research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition).The IRB allows the additional LPs because it believes, in this case, the research fulfills the following additional requirements:

- The risk represents a minor increase over minimal risk
- The research presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected dental, psychological, medical, social or educational situation
- The research is likely to yield generalizable knowledge about the subjects' disorder

or condition which is of vital importance for understanding or ameliorating it, and

- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians

Category of Research	Additional Protections
1. Research not involving more than minimal risk (45 CFR 46.404).	If appropriate, assure adequate provisions are made for soliciting assent of children and permission of parents or guardians.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to individual child subjects (46.405).	IRB must determine that: The research risk is justified by the anticipated benefit to the subjects The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition (46.406).	An IRB may approve the research only if it finds: The risk represents a minor increase over minimal risk The research presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected dental, psychological, medical, social or educational situation The research is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for understanding or ameliorating it, and Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare children (46.407).	An IRB must find that the research presents a reasonable opportunity to further understanding, prevention or alleviation of a serious problem affecting the health or welfare of children, and The Secretary, DHHS will convene a panel of experts in pertinent disciplines to review the research

Protections for child research subjects are justifiable and important. However, the NIH encourages the involvement of children in research on diseases that affect them. Generally, scientifically evaluated treatments are less available to children and often, medical treatments applied to children are based on results from testing on adults.

Therefore the NIH has guidelines entitled “NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.”

These NIH guidelines provide that children (defined in the guidelines as individuals under 21 years of age) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and/or ethical reasons not to include them. Therefore, if a research protocol excludes children, the IRB should document the reasons (the disease does not affect children, other research protocols exist to study the disease in children, etc.).

NIH IRB Review Standard

1. The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of knowledge that may reasonably be expected to result.
3. Risks to subjects are minimized.
4. Subject selection is equitable.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Additional safeguards are required for subjects likely to be vulnerable to coercion or undue influence.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.

NIH IRB Review Standard: *7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data.*	"Confidentiality" refers to the management of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure. Generally, "privacy" means having control over the extent, timing, and circumstances of sharing information (physical, intellectual, or behavioral) about oneself with others. Biomedical and behavioral research may invade the privacy of individuals or result in a breach of confidentiality. In certain circumstances, an invasion of privacy or breach of confidentiality may present a risk of serious harm to subjects as, for example, when a researcher obtains information about subjects that if disclosed by the researcher, would jeopardize their jobs or lead to their prosecution for criminal behavior. In other circumstances, such as observation and recording of public behavior (observing people at toll booths or ticket counters, etc.), the invasion of privacy may present little or no harm. The need for confidentiality exists in virtually all studies in which data are collected about identified subjects. In most research, assuring confidentiality is a matter of following some routine practices: • Substituting codes for personal identifiers • Properly disposing of computer sheets and other papers • Limiting access to identified data • Storing research records in locked cabinets • Impressing on research staff the importance of confidentiality. Most researchers are familiar with these routine precautions taken to maintain the confidentiality of data. **Example:** In keeping with procedures set forth in her IRB–approved protocol, a researcher keeps research records in a locked cabinet in her office. She mistakenly leaves the cabinet unlocked one afternoon when she goes to clinic. She returns to find the records in one entire drawer are missing. A massive search conducted by the campus police fails to find them. She reports the disappearance of the records to the IRB along with procedures for informing the subjects of the presumed theft. At a minimum, NIH IRBs should assure themselves that the protocol under review provided adequate measures to safeguard the confidentiality of research information to the extent possible. The types and stringency of these measures will depend on the type of information to be gathered in the study. In any case, guarantees of "absolute" confidentiality (for example, in the informed consent document) should be avoided; in fact, the limits of confidentiality should be clarified. For example, federal officials have the right to inspect research records, including informed consent documents and individual medical records, to ensure compliance with the rules and standards for their programs (i.e., FDA inspections of clinical trial records). Basic protections for NIH research and medical records are provided in the Federal Privacy Act. Copies of the Act are available from your IRB chair or OHSR. More elaborate procedures may be indicated in studies in which data are collected on sensitive matters such as sexual behavior, criminal activities, and genetic predisposition to disease. For example, your IRB may review research which could benefit from a certificate of confidentiality, More information about certificate of confidentiality is available from your IRB chair or OHSR. This completes the overview of the IRB review standards. There are a few other general considerations concerning protocol review with which you need to be familiar. • Investigators are expected to identify when ionizing radiation is used for research purposes, and IRBs, as well as the NIH Radiation Safety Committee, are expected to approve this use. • You should be familiar with the regulations of the Food and Drug Administration (FDA) if

	your IRB reviews research involving FDA-regulated investigational drugs or devices. Copies of the regulations are included in your IRBs standing operating procedures. • The IRB will discuss the special considerations that must be taken into account when reviewing research involving human subjects at international or domestic sites without federal wide assurances (FWAs)

Applying the IRB Review Standards

Experience and practice will help you develop an effective way to apply the review standards when reviewing research protocol.

NIH IRBs vary in their implementation of these standards. Some IRBs ask Principal Investigators (PIs) to address each of the review standards during their oral presentations at the time of initial review of their protocols. This is a particularly effective approach and saves time because the PI comes to the IRB with a clear oral description of the human subjects protection issues associated with the protocol

It is important for you to use the review standards, which were designed to assure, that during an NIH IRB's initial review of protocols, all regulatory requirements are discussed and documented in its minutes.

Summary Points

- NIH IRB review standards incorporate minimal regulatory requirements for the review and approval of research protocols
- The standards were developed to help NIH IRB members address these requirements methodically and consistently, and
- Time and experience will help you understand better how to apply the standards when reviewing research protocols

If you have any questions about the standards or how to apply them, ask your IRB Chair or call OHSR at 301-402-3444.

If you want to review the list of the NIH IRB review standards again, click **HERE**.

Conclusion

Understanding and appreciating the review standards will help you effectively consider and discuss the human subjects protection aspects of your research protocols. When presenting your protocols to an NIH IRB you should be prepared to address each of the standards in relation to your protocol.

If you do this, the IRB will have the benefit of your thinking on these human subjects aspects of your protocol; the PI's informed and well-reasoned opinions are valuable and important to IRBs.

The NIH believes that sound ethical practices go hand in hand with scientifically valid research involving human subjects.

Therefore, the NIH depends greatly on the knowledge and expertise of its PIs in both the scientific and human subjects protections dimensions of their clinical research activities.

If you have any questions about the NIH HRPP, NIH policies and/or the IRB review standards, you may contact your IRB chair or the Office of Human Subjects Research at 301-402-3444.

To conclude this section, take a look at some actual questions posed by Principal Investigators to Dr. Wichman at the end of her live presentations of this material. Click on the questions to view Dr. Wichman's answers.

When you're finished exploring these questions, click the Next button below to proceed to the test questions for this section. When you've answered the questions for this section, click the Submit button.

Is there an appeals process available to a PI if he or she has irreconcilable differences with their IRB?

QUESTION: "Irreconcilable differences between the IRB and the researcher, there's not an appeals process, is there?"

ANSWER: "There is not an appeals process. It is best for you to try to make a difference not irreconcilable. Investigators who understand and appreciate the IRB's roles and responsibilities are most likely to work effectively with them."

Would you comment on the rules for an exemption of studies from IRB Review?

QUESTION: "Would you comment on the rules for an exemption of studies from IRB Review?"

ANSWER: "Our office (the Office of Human Subjects Research) grants exemptions. The regulations recognize that there are some types of research involving human subjects that put them at low or no risk. Since IRBs review research from the vantage point of protecting human subjects, the regulations recognize that these low or no–risk activities do not need IRB review and approval."

"On the OHSR web site there is a form that you must fill out and send to us for review. If you have questions about whether your research activity is exempt, call us before you fill it out. Often if we think the research is not exempt we can guide you about ways it can be made exempt. For example, we can exempt your research on existing human samples if they are anonymized (but cannot if you maintain identifiers on the samples). As soon as we notify you that your research is exempt, you may begin."

"It's really in the researcher's best interest that there are some types of research activities that are exempt. For example, much of the work that you may want to do with stored samples may be exemptable if you can anonymize the samples. Our office grants exemptions, so if you have any questions, call us."

Would you comment on the certificates of confidentiality?

QUESTION: "Would you comment on the certificates of confidentiality?"

ANSWER: "A certificate of confidentiality is a federal government issuance. It doesn't just relate to federally funded research. When it was first thought up, it generally did apply to federally funded research and allowed investigators to apply for additional assurances of confidentiality against, for example, subpoena of information."

"It adds a little bit, but not absolute protection. Each institute should have a person who can help you decide whether a certificate is appropriate for your research. For example, in research involving drug use and some illegal behavior, it does offer some protection from access of those records to police, for example, or to Congress to some degree. Also, your IRB can help you decide if a certificate of confidentiality is appropriate for your protocol."

According to federal regulations, who is most appropriate to obtain informed consent?

QUESTION: "One of the issues we're struggling with has to do with delineating who can obtain informed consent formally and whether it needs to be a Principal Investigator or an Associate Investigator or whether the PI can designate someone who is not part of the protocol, and our Institute has taken one approach. I was just curious as to what you think the Federal Regulations would suggest and what advice you would have?"

ANSWER: "Well, the regulations do not address specifically who ought to obtain informed consent. Certainly the Principal Investigator is responsible for assuring that informed consent is obtained from subjects. He or she may delegate that to somebody, but the PI should say who is going to be getting informed consent, and should discuss that with the IRB."

"It is important, I think, in some types of protocols, that the PI always obtain informed consent. In others, he or she may delegate that to another investigator or sometimes to a nurse. Although it is acceptable to authorize someone else to do it, the IRB should agree that that person is both appropriate and adequately trained."

"There is a general trend, a popular notion, that PIs are not the best people to get informed consent because they may be too biased. I don't agree with that. I think our investigators are both the best educated and well–placed to obtain informed consent. You might want to have someone else who is not a member of the research team discuss the protocol or the subject's concerns, but I still think Principal Investigators and Associated Investigators are best placed to promote informed decision making."

Should a Data Safety Monitoring Board be used for double blind, placebo–controlled, interventional trials?

QUESTION: "One of the previous speakers stated that the Data Safety Monitoring Board must be used for all double blind placebo controlled interventional trials, and you described that the Data Safety Monitoring Board may be used in discussion with the IRB. Can you clear this up?"

ANSWER: "The guidelines for Data Safety and Monitoring Boards are provided in OHSR Information sheet #18 on our website. I think the general trend is toward close monitoring of data from double blind placebo control studies. An IRB could do the Data Safety and Monitoring, but I think each Institute is being asked to come up with an approach to DSMB's."

"I think if you are going to design a double blind placebo–controlled study to be conducted in the Clinical Center, read the information sheet and discuss it with your Clinical Director. It is possible you could articulate a scenario where an Independent DSMB wouldn't be appropriate, but it is your responsibility to provide this justification to the IRB for its consideration."

Can you address the issue of implicit coercion in obtaining informed consent?

QUESTION: "Can you just address the issue of **implicit coercion** in obtaining informed consent for example, from a patient with a rapidly fatal illness, who is impoverished or uninsured, or comes from a country that has no medical resources. I mean, how is that situation different from a prisoner, where there's just an assumption of implicit coercion, because of the lack of alternatives?"

ANSWER: "That's a tough question. It's really tough when people are very ill, when they're dying, when they perceive their voluntariness of a decision so narrowed. Then add on to that the lack of resources to get care elsewhere."

"This is exactly the situation we experienced in the mid–1980s when HIV infected children, many of whom were poor or foster children, came to the CC to participate in research. They had no medical care, really, or if they did have medical care it certainly wasn't informed by knowledge that was accruing about HIV."

"When we do research involving very ill people we ought to acknowledge that for a variety of reasons they may be vulnerable to coercion. For example, their choices are often severely restricted. We need to make serious efforts to promote informed decision-making by all, but particularly vulnerable, research participants. Sometimes protections additional to informed consent may be appropriate. For example, sometimes it may be helpful to have an intermediary talk with research subjects in order to evaluate their understanding and appreciation of the situation. For each research protocol an NIH IRB reviews, it is expected to address the issue of whether research subjects may be vulnerable to coercion or undue influence, so the issue is confronted often by our researchers and IRBs."

Roles and Responsibilities of the Investigator

Authored by Heather Bridge and Juan J. L. Lertora, M.D., Ph.D.

Introduction

Clinical research is sponsored by the National Institutes of Health (NIH) and is conducted at the NIH Clinical Center as a core component of the various NIH institutes and centers' (ICs) scientific mission of creating new knowledge about, and developing new treatments for human diseases. Clinical research is a complex and demanding process, usually conducted as a team effort of physicians, clinical and basic scientists, clinical research nurses and pharmacists, and study coordinators and biostatisticians, with the support of administrative and laboratory personnel.

Every protocol developed to study a disease and/or a new treatment modality, must have a designated Principal Investigator (PI), who is ultimately responsible for: the proper scientific design of the clinical trial; study implementation; proper data collection and documentation; compliance with regulatory and ethical mandates regarding the use of human subjects in research; and informed consent procedures. Additionally, the PI must adhere to the reporting requirements of an Institutional Review Board (IRB), the study sponsor (NIH, private foundation, pharmaceutical industry, etc.), and the Food and Drug Administration (FDA) when dealing with investigational new drugs or devices. Depending on where and how the study is conducted, the PI must also be familiar and comply with any number of additional regulatory bodies such as Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO) and Office of Human Research Protections (OHRP).

The NIH Clinical Center, in conjunction with other NIH ICs, can provide new clinical investigators with a variety of resources intended to assist in the writing of a comprehensive clinical trial protocol and to guide the investigator through all the required scientific, regulatory, safety, and ethical review of the proposed study. This educational module was developed to highlight the roles and responsibilities of the Principal Investigator as the person ultimately responsible for all aspects of conducting a clinical trial and assuring the safety of human subjects research.

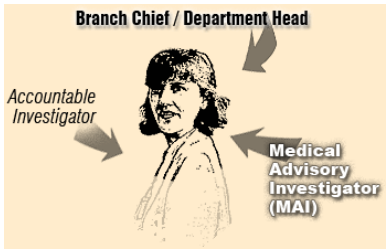
Section Content

This section reviews the following topics relating to the responsibilities of Principal Investigators conducting clinical research:

- Resources for Investigators
- Qualifications of the Principal Investigator
- Responsibilities of the Principal Investigator
- Protocol Design
- The Protocol Approval Process
- Effective Informed Consent
- Collection and Verification of Data
- Audits and Monitoring
- Collaboration

This section, along with the quiz at the end, will take approximately 30 minutes to complete.

Resources for Investigators



The rules that govern the conduct of clinical research are often in flux, with new and changing policies occurring frequently. This can lead to confusion about how to interpret and best apply these changes to the conduct of your study. NIH provides an infrastructure to support investigators in navigating this complex issue. Senior investigators are a good source of information and mentorship. Your Lab Chief is a good source of information. Additionally, each protocol may also be assigned the following senior investigators to help oversee and guide the Principal Investigator:

1. Branch Chief/Department Head: The Branch Chief signs off on initial and continuing reviews of protocols and is a valuable source of information.
2. Accountable Investigator: An Accountable Investigator is defined as a tenure or tenure-track investigator who is responsible and accountable for the scientific quality and the expenditure of resources for the conduct of a protocol. In some ICs, that responsibility is carried by the Branch Chief or Department Head.
3. Medical Advisory Investigator (MAI): A Medical Advisory Investigator is assigned to a protocol, when the PI is not a physician or when the Institute Clinical Director, IRB, or IC Director considers it warranted. The MAI must be a member of the junior or senior medical staff and is responsible for assisting the PI in developing clinical aspects of the protocol and consulting with the PI on clinical matters.

For links to key offices and policy sources here at the NIH, please see the "*Resources for Investigators*" menu item on the Main Menu page of this course.

Qualifications of the Principal Investigator

Let's take a look at the qualifications of a Principal Investigator. Since you are responsible for the clinical, administrative and regulatory duties of the trial; you will need the following skills necessary to conduct a successful trial:

- Adequate resources: The ability to assess and have in place, the appropriate infrastructure, subjects, time, staff and education, to properly conduct the trial;
- Medical Management of Subjects: The ability to manage the care for the subjects yourself or with the assistance of the MAI;
- Good Clinical Practice (GCP): When conducting an intervention trial (drug or device), familiarity with the appropriate use of the product or device that you are testing and compliance with Good Clinical Practice;
- Informed Consent: The ability to assure effective informed consent has been obtained by yourself or by qualified study staff;
- Data Collection and Analysis: The knowledge and organization to collect, maintain and analyze the data and specimens collected on the study and leveraging the expertise of a biostatistician in the early stages of protocol development.

These qualifications translate into a great deal of responsibility; however, there's even more.

Responsibilities of the Principal Investigator

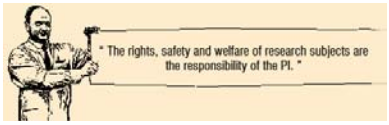
As a Principal Investigator you are accountable for the following:

Adhering to Regulations and Policies

You are expected to understand your responsibilities as they relate to regulations and internal institutional policies:

- Compliance with the Common Rule (45 CFR Part 46);
- Compliance with Good Clinical Practice guidelines (ICH E6, FDA GCP);
- Compliance with the Institutional Review Board (IRB), including initial and continuing review at intervals appropriate to the degree of risk and amendments to the protocol, as determined by the IRB;
- Compliance with the policies of the NIH Office of Human Subjects Research (OHSR), including those relating to the use of human specimens and data;
- Compliance with applicable policies of the Food and Drug Administration (FDA), including those relating to the protection of human subjects;
- Compliance with the protocol without deviation;
- Reporting Serious Adverse and Unanticipated Events in the appropriate timeframes;
- Complying with the "*Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH*" (3/2008) and distributing the "NIH IRP Conflict of Interest Guide" to all investigators, including non-NIH investigators;
- Cooperation with monitoring and auditing (21 CFR 312);
- Compliance with the Medical Administrative Series (MAS) Policies, when conducting research at the NIH Clinical Center;
- Depending on where and how the protocol is being conducted, complying with other institutional policies or international regulatory bodies such as CIOMS, WHO and the Federal Wide Assurance (FWA).

Protecting Human Subjects



The rights, safety and welfare of research subjects are the responsibility of the PI. The PI ensures that participants entered in the study are eligible for the interventions or observations described in the protocol, and that interventions are consistent with sound research design. You are expected to understand and implement regulations and procedures for the protection of human subjects.

- **Trial Registry:** All NIH intramural trials must be registered on ClinicalTrials.gov. In addition to being a potential source of recruitment, the registry is required by the International Committee of Medical Journal Editors (ICMJE) for publication. Note that Office of Protocol Services will register your trial for you, taking the information from the Form 1195 (*Initial Review Application*), at the time of initial review approval processing.
- **Subject Selection:** A well written protocol with careful subject selection and justification for exclusion of any protected class of subjects, protects subjects from potentially unnecessary or harmful exposure and avoids selection bias. It is the responsibility of the PI to ensure that foreseeable risks be weighed against the benefits, and that the benefits justify the risks. The PI must also ensure that any known risks are minimized to the greatest extent possible.
- **Informed Consent:** A critical component of human subjects protection is to provide full, clear and easy-to-comprehend information about a protocol to a subject or their legally authorized representative (LAR), and after doing so, to obtain their informed consent. Assent is also essential for minors, who are able to comprehend the concept of research. Consent/Assent should be freely given by subjects or their LAR prior to participation in any research activities.
- **Confidentiality:** Confidentiality of research data, that could identify subjects or their personal information, should be maintained to protect subjects from any potential employment, societal, legal or insurance harm.

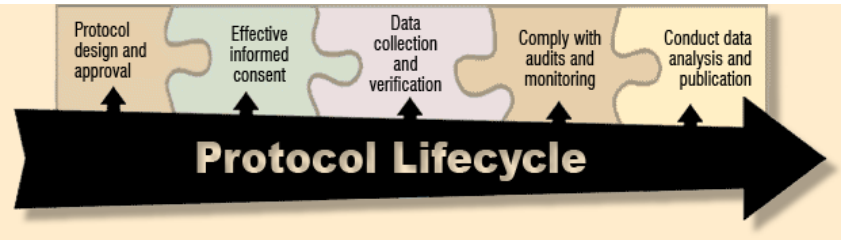
- **Safety Monitoring/Reporting:** A well designed safety monitoring plan and prompt reporting is designed to protect subjects in the case of unanticipated events.
- **Publication:** To share valuable scientific information resulting from your research with society and your subjects.

Managing the Protocol Lifecycle

As a Principal Investigator you have responsibilities before, during and after the trial is completed for:

- Protocol design and approval
- Effective informed consent
- Data collection and verification
- Comply with audits and monitoring
- Conduct data analysis and publication

Let's take a look at how these responsibilities break down.



Protocol Design

Your first responsibility as a PI is to prepare the protocol document, which includes administrative and research requirements. A clinical protocol is a research plan, not a general guide to your best clinical judgment. Additionally, you should design your protocol with the involvement of a statistician to assure optimal design and adequate power to answer the hypotheses.

Include the following sections in your protocol:

- Précis
- Introduction
- Objectives
- Inclusion and Exclusion Criteria
- Plan for Monitoring Subjects and Criteria for Withdrawal of Subjects from the Study
- Analysis of the Study
- Human Subject Protections
    - Rationale for Subject Selection
    - Recruitment Plan and Procedures
    - Justify the Exclusion of Women, Minorities and Children (if applicable)
    - Evaluation of Benefits and Risks/Discomforts of Participation
    - Description of the Consent/Assent Process
    - Plan for Maintaining Privacy and Confidentiality of Subject Records
- Adverse Event Reporting Plan
- Data Safety Monitoring Plan
- Protocol Monitoring Plan
- Data Management Plan
- Plan for Research Use and Storage of Human Samples, Specimens or Data
- Remuneration/Compensation
- Scientific References

There may be protocol authoring tools available to you to assist in the development process, please check with your Clinical Director or Lab Chief to see what resources your Institute may offer, (for example, *ProtoType* or protocol templates in use at various ICs).

The Protocol Approval Process

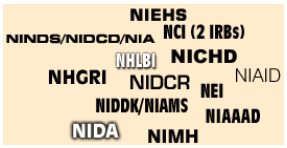
The PI is responsible for assuring that the protocol obtains the necessary regulatory, scientific and human subjects safety reviews, and that the final document is consistent with stipulations or recommendations.

In addition to the protocol there are several other items that must accompany the protocol as it goes through the approval process:

- NIH Form 1195: This Initial Review Application is a required form that summarizes key protocol demographics and includes required information for registering the protocol on the National Library of Medicine's ClinicalTrials.gov registry.
- Toxicity Tables (if applicable)
- Investigator Brochure (if applicable)
- "Clearance of NIH Investigator Personal Financial Holdings by IC Ethics Office" (PFH) Form signed by your institute Deputy Ethics Counselor which clears NIH employees to participate in the protocol based on their personal financial holdings. This applies to new protocols, continuing reviews and amendments involving investigators, or new treatments/devices.

There are a number of reviews that may also need to take place in order for your protocol to be approved before you can open to enrollment of subjects:

- **Scientific Review:** Each Institute is responsible for ensuring rigorous scientific review of its protocols before review by the IRB. Mechanisms of review vary, but generally they are performed by a committee that includes the Institute's Scientific and Clinical Directors and a staff member from the Institute's extramural program.
- **Institutional Biosafety/Recombinant DNA Advisory Committees:** Oversight for clinical trials involving gene transfer is performed by the Office of Biotechnology Activities (OBA). NIH requires that protocols involving gene transfer be reviewed by the Recombinant DNA Advisory Committee (RAC) and approved by the Institutional Biosafety Committee (IBC). No research participants may be enrolled in the study until the RAC review process has been completed and the investigator has obtained IBC approval from the clinical trial site, IRB approval, and all applicable regulatory authorizations. The protocol must comply with the "NIH Guidelines;" to ensure this, the protocol must undergo review and approval from the following committees:
- **RAC:** A Federal advisory committee that makes recommendations to NIH on matters concerning recombinant DNA. Among other activities, the RAC reviews human gene transfer protocols registered with NIH and selects a subset for public review at a quarterly RAC meeting. The outcome of the public meeting is a set of recommendations sent to the investigator, the FDA, the IBC, and the IRB.
- **IBC:** An institutional review body that reviews and approves research subject to NIH guidelines, including the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into any human research participants. IBC approval of human gene transfer research must come after the RAC review process is completed.



- **Institutional Review Board (IRB):** The primary mandate of an IRB is to protect and safeguard the rights and welfare of human research subjects. All human subjects research protocols require prospective (initial) and continuing review by the IRB for the institute or center where the research is being sponsored and at each study site where the research will be conducted. If the study is being conducted elsewhere, including international sites, it will also require approval by the local Ethics Committee. Additionally, all IRBs/ECs must be covered under the Federal Wide Assurance (FWA). To locate the FWA number for institutions you will be working with see the Office of Human Subject Protections (OHRP) website.
- **Deputy Ethics Counselor Reviews:** The Principal Investigator is responsible for ensuring that all ethics clearances have been obtained and are current, and that the "Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH" (NIH COI Guide) has been distributed to all NIH and nonNIH investigators. NIH employees designated as clinical investigators, regardless of whether they are required to file the SF-278 or OGE-450, must be cleared by the IC DEC. Clinical investigators are those employees who participate in the conduct of clinical protocols and whose names are listed on the protocol application, NIH Forms 1195 and 1195-1. All designated clinical investigators who are employees of the NIH must file a form 717 detailing personal financial holdings in pharmaceutical, biotechnology, or medical device companies. These holdings must be updated every six months with the IC Deputy Ethics Counselor.
- At the time of Initial or Continuing Review and for those Amendments where an NIH investigator is being added to the protocol or there is a change to the IND/IDE for the protocol, a conflict of interest clearance must take place by submitting the "*Clearance of Personal Financial Holdings*" form to your IC Ethics Office.
- The Principal Investigator is responsible to assure that all non-NIH investigators have received and reviewed the NIH COI Guide, "*A Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH*" (3/2008).
- Additionally, all consent forms must contain the NIH-required conflict of interest statement(s).
- **Investigational New Drug/Device (IND/IDE) Application:** For protocols involving new or novel use of existing drugs or devices, for more information speak with your Sponsor regarding submission to the FDA. You will learn more about this process when you complete the "*Regulatory Issues*" module of this course. Additionally, you may also take, "*Introduction to the Regulatory Process for Clinical Investigators*" online training course.
- **Radiation Safety Committee (RSC) (Form 88-23):** if research radiation will take place, submit this form to the RSC for review;
- **Determination of Human Subjects Research/Exempt Studies:** If you are unsure if your research constitutes human subjects research or if you believe your research might meet the criteria for being considered an "exempt" study for purposes of 45 CFR Part 46, contact the Office of Human Subject Research (OHSR). The OHSR website is a good source of regulatory and ethical guidelines for conducting research at the NIH. The OHSR website: **http://ohsr.od.nih.gov/**.
- **Use of Coded or Anonymized Human Specimens or Data:** You should contact OHSR if you are doing research with coded or de-identified human samples or data and do not know all of the rules relating to the use of such items. Approval of OHSR or the IRB is required, before you are permitted to conduct such studies.
- **Other Reviews:** that may be required by your institute or center:
- **Regulatory Review:** ICs may require a separate regulatory review for protocols that involve an IND/IDE. Please check with your lab/branch chief to see if this applies at your IC.
- **DSMB Review and Initial Monitoring Visit:** In addition to reviews, several monitoring activities may be required before the protocol opens to enrollment (see "Audits and Monitoring" below):
- Data Safety Monitoring Board (DSMB) - if your protocol requires that a DSMB be convened.
- Initial Monitoring Visit- if your protocol requires monitoring, you may need an initial site visit prior to opening to enrollment.
- **Agreements:** If you will be collaborating with outside institutions or scientists, you will need to ensure that the appropriate agreements are in place (see "Collaborating with Others" below:
- Clinical Trial Agreement (CTA), Material Transfer Agreement (MTA), or Collaborative Research

Agreement (CRA): Please check with your IC's Office of Technology Development (OTD) or the NIH Office of Technology Transfer (OTT).

- **Certificate of Confidentiality:** If your protocol will be collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation; you should seek a Certificate of Confidentiality (CoC) to protect your subjects. Contact the Certificate Coordinator for your IC for more information.

After Approval

After initial approval is achieved your responsibilities continue. When the trial begins subject accrual, the PI has the final responsibility that the trial be conducted as written, monitored for outcomes and adverse events, and analyzed at regular intervals.

As your trial progresses, you must maintain communication with your IRB. You must inform the IRB in the event of the following:

- **Adverse or Unanticipated Events** - A death on study must be reported verbally to the Clinical Director as soon as possible. Unless otherwise specified on the protocol and approved by the IRB, the PI must report all serious adverse events (SAE) in writing as soon as possible, but no more than seven (7) calendar days for death or life-threatening adverse events and within 15 days for all others. Adverse Events that do not rise to the level of a SAE must be reported at the time of continuing review. If you are working with an IND or IDE, in addition to these reporting requirements your Sponsor/the FDA will have additional reporting timeframes that must be followed.

- **Amendment to the Protocol** - Any change to the conduct of the study, the protocol or the consent(s), such as a change in eligibility requirements or exclusion criteria as a result of unanticipated adverse events, must be submitted as an amendment to the IRB for approval before any changes in protocol activities may take place; except when necessary to eliminate apparent immediate hazards to the subject. In this case, the PI may take immediate action but must subsequently notify the IRB and amend the protocol.
- **Protocol Violations** - A protocol violation is any change or divergence from the study design or procedures of a research protocol that is under the investigator's control that has not been approved by the IRB. The violation may affect the subject's rights, safety, or well being, and/or the completeness, accuracy and reliability of the study data. Protocol violations must be reported by the Principal Investigator to the IRB upon discovery of the occurrence.

Each year, you must complete a continuing review. Continuing review and approval must be completed by the expiration date; otherwise IRB approval for the protocol expires. Research may not be conducted absent IRB approval. Research activities involving identifiable human specimens and identifiable data must occur under an open protocol, either the protocol which is the source of the specimens and data or another NIH protocol. Federal regulations and NIH policy do not provide for exceptions to the requirement for continuing review, therefore **failure by the PI to obtain IRB review by the expiration date is a serious matter that will lead to automatic termination of the protocol**. Upon notification of termination, the PI must submit proposed procedures for withdrawal of currently enrolled subjects that takes into consideration their rights, safety and welfare, to the IRB. Reactivation of a terminated study requires submission of a new initial review to the IRB for approval.

Minimum required documentation for a continuing review is:

- A completed NIH 1195-1 ("*Clinical Research Protocol Continuing Review Application*");
- The protocol, with version and page numbers, and consolidation of all amendments since its last review;
- Up-to-date protocol consent document(s);
- Inclusion Enrollment Report;
- A summary of the FDA annual report, if applicable;
- Conflict of interest clearance from the IC Deputy Ethics Counselor;
- Any additional IC requirements (e.g., checklists) and
- An annual report addressing the following:
    - a brief narrative explaining current progress/findings from the research;
    - a summary of any amendments made to the research protocol since the last review;
    - the number of subjects accrued, consistent with the Inclusion Enrollment Report
    - a summary of adverse events and any unanticipated problems involving risks to subjects or others;
    - a summary of subject withdrawals from the research;
    - any reports of complaints about the research since the last IRB review;
    - any relevant multi-center reports;
    - any data and safety monitoring board reports;
    - any information from the literature or from this or similar research that might affect the IRB's evaluation of the risk/benefit analysis of human subjects involved in this protocol; and
    - reason(s) for continuing the study;

Continuing review applications that do not include these documents will not be accepted for review by an NIH IRB.

Upon Completion

Once you have reached the completion date of the protocol, you must report the results of your trial on ClinicalTrials.gov. When you first opened your protocol, NIH Office of Protocol Services registered your trial on ClinicalTrials.gov. Effective September 2008 (*Public Law 110-85, Sec. 801*), most interventional (IND/IDE, e.g., drug/device/biologic) clinical trials (ongoing as of 9/27/2007 or after) and, phases 2-4, with at least one clinical site in the United States, are required to report basic outcome results on ClinicalTrials.gov. The sponsor or grantee, (or the principal investigator, if designated by the Sponsor or grantee), is responsible for reporting the results. It is strongly recommended that the investigator work with the study statistician in preparation for, and reporting of the basic results. It should be determined early in the development cycle who the responsible party will be. In many cases the principal investigator will be the responsible party. However, if you are not sure if you are the responsible party for reporting the results of your trial, check with your Lab/Branch Chief for more information.

The timeframe for reporting is within one year of the completion date (date the last primary outcome data element was collected) or within 30 days of approval of the drug, device or biologic, in the United States by the FDA. Submission of results data may be delayed under particular circumstances (see http://prsinfo.clinicaltrials.gov/DelayedSubmission.html). There may be penalties for not reporting within the required time frame including: notices of non-compliance, civil monetary penalties up to $10,000/day and the withholding of NIH funding (grants).

Effective September 2009, the Basic Results Reporting Law will be expanded to include reporting of adverse events. The expanded reporting will include the number of expected and unexpected serious, or frequent (>5%) non-serious adverse events by study arm and by organ system. As the effective date approaches for this new regulation, more details will be provided by your IC or the NIH. The important thing for you to know is that NIH principal investigators are expected to comply with these regulations when applicable.

Effective Informed Consent

Investigators are responsible for informing potential research subjects of the nature of the study, the risks and benefits of, and the alternatives to participation and all other information necessary for the subjects to make a considered decision whether or not to participate. Investigators are responsible for assessing that the subject understands the information provided and gives voluntary consent, free of coercion or undue influence.

Your subjects must have adequate information about the study you want them to participate in, stated in simple language that is easy for them to understand. You must provide them with an IRB-approved, written consent form, written at no more than the eighth grade level, which contains the following:

- A statement that the study involves research;
- An explanation of the purpose of the research, an invitation to participate and explanation of why the subject was selected, and the expected duration of the subject's participation;
- A description of procedures to be followed and identification of which procedures are investigational and which might be provided as standard care to the subject in another setting. Use of research methods such as randomization and placebo controls should be explained;
- A description of the foreseeable risks or discomforts to the subject, an estimate of their probability and magnitude, and a description of what steps will be taken to prevent or minimize them, as well as acknowledgement of potentially unforeseeable risks;
- A description of benefits to the subject or others that may reasonably be expected from the research, and an estimate of their likelihood;

You must provide research subjects with an IRB-approved, written consent form, written at no more than the eighth grade level, which contains the following:

- A disclosure of any appropriate alternatives procedures or courses of treatment that might be advantageous to the subject;
- A statement describing to what extent records will be kept confidential, including examples of who may have access to research records such as hospital personnel, the FDA and drug sponsors;
- For research involving more than minimal risk, an explanation and description of compensation and any medical treatments that are available if subjects are injured through participation; where further information can be obtained and whom to contact in the event of a research-related injury;
- Whom to contact for answers to questions about the research and the subject's rights;
- A statement that research is voluntary and that refusal to participate or a decision to withdraw at any time will involve no penalty or loss of benefits to which the subject is otherwise entitled;
- A concluding statement indicating that the subject making a decision whether or not to participate, and that his/her signature indicates that s/he has decided to participate having read and discussed the information presented.

In addition to the required elements listed on the previous pages, there are a number of additional elements that may be required for complete consent. For more information refer to the MAS Policy M77-2.

Other important information or policies that you should familiarize yourself with are:

- Obtaining oral informed consent, short-form consent for non-English Speaking subjects and Assent from minors.
- Working with Legally Appointed Representatives (LAR) for subjects unable to provide consent.

The Department of Bioethics Consult Service can assist you in assessing a subject's ability to comprehend consent and to resolve difficult ethical issues involving potential participation of subjects.

Collection and Verification of Data

Documentation is crucial. Source documentation includes original medical records, documents and data, for example: medical records, pharmacy dispensing records, laboratory data, subject diaries or checklists. It is from your source documentation that you will collect your research data. The research data are captured on Case Report Forms (CRFs). A CRF is a paper or electronic document designed to capture the necessary research or safety data required to perform analysis or for reporting. These are the data you will report to your sponsor. You must carefully monitor data collection and verification. Both CRF and source documentation may be audited and reviewed by Monitors and Auditors.

For best practices regarding documentation (source or CRFs), refer to the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Guidelines. You must ensure the following:

- Accuracy, timeliness and completeness of your CRFs
- Consistency of your CRFs with source documents
- Changes to your CRFs are dated, initialed and explained
- Original entries are not obscured (to provide an audit trail)
- Documents, in a study involving new agents, are retained for two years beyond the date of the last approval of a marketing application or discontinuation of the study

Additionally, you **must** protect your research data and make sure it is held confidential to protect the interests of your research and your subjects' confidentiality. If you maintain a database of your research data it must have appropriate protections such as limited access and password protection.

If you are conducting your research at the NIH Clinical Center, you will encounter the Clinical Research Information System or CRIS. CRIS is the overall term used for the electronic medical record utilized for all patients who come to the NIH campus. It incorporates physician order entry, documentation, and results and document retrieval, and includes interfaces to several important ancillary systems such as Radiology, Laboratory and Pharmacy.

CRIS provides benefits for researchers and includes the ability to:

- Collect data once for both research and clinical care - based on the protocol
- Provide ready access to results and documentation for patient care and research
- Visualize trends over time for clinical results and observations
- Ensure standardized care and data collection with protocol order sets
- Facilitate clinical decision support for patient care
- Export data to institute research systems and repositories
- Support administrative oversight of patient care and resource utilization

Additionally, your IC may have other electronic systems that support your research, check with your Branch Chief for more information.

Audits and Monitoring

Audits are essential to quality care and good clinical practice. Audits examine documentation; compare it to your protocol and where necessary evaluates your procedures. Audits whether internal or external are a rigorous process by their nature. They help uncover problems, their causes and help you look for solutions.

There are two kinds of audits:

- Internal audits - These are done from within your institution and judge the PI
- External audits - These are done by reviewers outside of your institution and judge both the PI and the institution

Audits and Monitoring

Audit- Internal

An internal audit evaluates your protocol progress, accrual, eligibility and evaluability rates. Most internal audits uncover sins of omission rather than commission. Here are some examples of problems that were uncovered in internal audits, the reasons for the problems and solutions that fixed the problems:

Problem: Signed informed consents are not current

Cause: Outdated paper copies on file in the clinic

Solution: Replace paper consents with Web-based documents that can be updated and downloaded in real time

Problem: Subjects found to be technically ineligible for medically unimportant reasons, such as slight increase in serum creatinine

Cause: The protocol mandated absolutely normal values, which made the eligibility criteria overly restrictive

Solution: Amend the protocol to make it medically logical

Problem: Tests required by the protocol are not performed

Cause: The PI thinks they are unimportant

Solution: Require only what is needed as the protocol is developed and submitted for review, otherwise the audit will find a violation

Audit - External

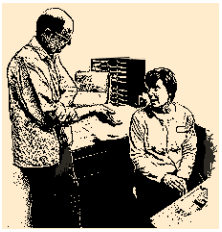
External audits evaluate both the PI and the Institution by comparing the source documentation with the research record as well as auditing regulatory compliance. Auditors cannot read minds or read between the lines, so everything must be accurately documented. This process requires a site visit by an outside audit team. This team looks for the following in your documentation:

- Accuracy
- Subject eligibility
- Informed consent (current / dated / signed)
- Scheduling / interpretation of diagnostic images
- Pathology compliance
- Operative reports
- Laboratory data
- IRB reviews of protocols and consents, including initial approval, amendments, annual reports, adverse events reports, special patient exemptions, and protocol violations
- Investigational drug logs

The review team may be on your doorstep one day. They may find only minor deficiencies or they may reveal major deficiencies where conclusions are questionable or there is significant regulatory noncompliance. Some major deficiencies that have been uncovered in external audits include:

- There was no documentation of initial review and approval
- Subject registration approval / treatment occurred before IRB approval
- There was missing or expired re-approval
- Subject was being treated during expired re-approval
- Serious adverse events were not reported to IRB
- There was lack of documentation of IRB approval for an amendment
- Omission of a required element
- Omission of a known risk or side effect
- Accumulation of minor deficiencies constituting a protocol violation

Collaboration



Collaboration is an important component of clinical research. Collaboration provides an exciting opportunity for NIH investigators to join with their colleagues from industry and academia in the joint pursuit of common research goals. Government scientists can leverage their own research resources, as well as serve the larger mission of NIH, to facilitate the development and commercialization of health-care pharmaceuticals and products. However, issues over intellectual property, publication, confidentiality and royalties can arise if not handled properly. As the PI, you should familiarize yourself with agreements designed to protect your and the NIH's interests before you engage in collaborative research: Cooperative Research and Development Agreements (CRADAs), Material Transfer Agreements (MTAs), Clinical Trial Agreements (CTAs) and Collaborative Research Agreements (CRAs). Each NIH institute has a Technology Development Coordinator (TDC) who should be consulted at an early stage of collaboration by the company and the NIH investigator to assist in identifying and developing the proper documents and obtaining the required approvals. Some commonly used agreements are the:

- **Cooperative Research and Development Agreement (CRADA):** The purpose of a CRADA is to make Government facilities, intellectual property, and expertise available for collaborative interactions, and where applicable, to further the development of scientific and technological knowledge into useful, marketable products.
- **Material Transfer Agreement (MTA):** A MTA generally is utilized when any proprietary material is exchanged, and when the receiving party intends to use it for his/her own research purposes. Neither rights in intellectual property nor rights for commercial purposes may be granted under this type of agreement. MTAs define the terms and conditions under which the recipients of materials, provided by either the NIH scientist or the other party, may use the materials. Included in the MTA are the requirements that the materials be used for research purposes only and that the materials cannot be used in human subjects.

Special MTAs can be developed for the use of materials to be used in human subjects research. The NIH also requires that all materials received by their scientists originating from humans be collected in compliance with 45 CFR 46, the Common Rule.

- **Clinical Trial Agreement (CTA):** To be utilized when collaborating with a non-NIH Sponsor/IND holder who is providing study drug or other valuable clinical resources.
- **Confidential Disclosure Agreement (CDA):** Used to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between the IC and the collaborator.
- **Collaboration Research Agreement (CRA):** Used to define responsibilities and obligations of the IC and collaborator for a collaborative research project.

Before you engage in collaboration, contact your IC's Technology Development Coordinator (TDC) to ensure that you have the correct agreements in place to protect your and the NIH's interests, while furthering the interests of science. To find your Technology Development Coordinator (TDC): **http://www.ott.nih.gov/nih_staff/tdc.aspx**.

Conclusions

- You must be qualified to be a Principal Investigator
- You must comply with applicable policies and regulations
- As the PI you are accountable for the conduct of the study including:
    - Protocol design, implementation and registration
    - Provision of human subject protection
    - Effective informed consent
    - Data collection and verification
    - Adequate infrastructure to conduct the study
    - Implementation and documentation of your study as though it might be audited
    - Reporting the basic results and adverse events on ClinicalTrials.gov

Regulatory Issues

Originally based on a presentation by Jay Siegal, M.D. and updated by Gilbert J. Burckart, Pharm.D.

Introduction

This section will help you understand the FDA oversight of clinical research and the FDA regulations and guidelines that are critical to the ethical and safe design and implementation of clinical research within FDA jurisdiction. After reviewing this section you should have an improved understanding of:

- The FDA organizational structure as it pertains to clinical research involving drugs, biologics or devices
- Applicable regulations and guidance for NIH Investigators and sponsors
- FDA adverse experience reporting requirements
- The IND process for studying new investigational drugs
- Investigators' and sponsors' responsibilities under FDA regulations
- ICH Guideline for Good Clinical Practice
- Where to go for help

This section, along with the quiz at the end, will take approximately 30 minutes to complete.

Test Your Knowledge

Before we discuss some of the regulatory issues surrounding human subject research, test your knowledge with the question below.

The FDA Administration Amendment Act of 2007 was an important milestone for the Agency in that it:

A. Gives the FDA the authority to mandate, rather to just request, that post-marketing studies be conducted to improve drug safety.
B. Requires that a registry be established of clinical trial information for those agents beyond phase 1.
C. Requires that pediatric studies be conducted with all new drugs.
D. a and b.
E. a, b and c.

Answer

The FDA Administration Amendment Act of 2007 was an important milestone for the Agency in that it:

A. Gives the FDA the authority to mandate, rather to just request, that post-marketing studies be conducted to improve drug safety.
B. Requires that a registry be established of clinical trial information for those agents beyond phase 1.
C. Requires that pediatric studies be conducted with all new drugs.
D. a and b.
E. a, b and c.

The History of the FDA

FDA is the oldest federal agency dedicated to consumer protection and is a scientific, regulatory, and public health agency that oversees products accounting for 254 of every dollar spent by Americans. Almost any food, cosmetic, drug, radiation product, medical device or biologic product you can think of is regulated by the FDA.

The FDA has a colorful history, and celebrated its 100th anniversary in 2006. The history of the Agency can be reviewed at http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm The history of the FDA is closely linked to ongoing legislation and activities of the agency. The evolution of the FDA is not static, as evidenced by legislation as recently as September of 2007 which is discussed below.

Inside the FDA

The Food and Drug Administration provides oversight of legal requirements for trials that use FDA regulated products and human subjects. Most human medical products, including biologics, drugs and devices are regulated by three FDA centers:

- Center for Biologics Evaluation and Research (CBER)
  Offices for Therapeutics; Vaccines; Blood; Cell; Tissue, and Gene Therapy
- Center for Drugs Evaluation and Research (CDER)
  Product divisions largely by medical specialty
- Center for Devices and Radiological Health (CDRH)
  Divisions by indication

Other major divisions of the FDA include:

- **Center for Food Safety and Applied Nutrition (CFSAN)**
- **Center for Veterinary Medicine (CVM)**
- **National Center for Toxicological Research (NCTR)**
- **Office of the Commissioner (OC)**
- **Office of Regulatory Affairs (ORA)**

To read more about the organization of the FDA, go to:

http://www.fda.gov/opacom/7org.html

Important Laws

FDA regulations are based on law. Regulations are delegated legislation in that the Agency promulgates regulations to carry out laws. The key laws that give FDA oversight over some clinical research are as follows:

The Federal Food, Drug and Cosmetic Act
Section 505 [351] - "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless approval of an application..."

The Food and Drugs Act of 1906 did not require pre-market approval, so the FD&C Act of 1938 was a major advance. Numerous amendments have been made to the FD&C Act (see **http://www.fda.gov/opacom/laws/default.htm#amendments**), and the most recent was the Food and Drug Administration Amendment Act of 2007, or FDAAA. This legislation was enacted on September 27, 2007. FDAAA made substantial changes to the ability of the FDA to improve drug safety, including the ability to require (not just request) that post-marketing studies be conducted. The FDA and the NIH will also work together on a FDAAA-mandated national registry for clinical drug trials and the results of those trials. The NIH registers all non-Phase I trials on the National Library of Medicine (NLM) **ClinicalTrials.gov** site.

At the same time, the U.S. Congress renewed two important laws relating to pediatric drug use; the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

Best Pharmaceuticals for Children Act (BPCA) – encourages more studies in children and promotes the development of treatments for children. The FDA may issue written requests for companies to conduct studies with products that children would benefit from.

Pediatric Research Equity Act (PREA) – continues FDA's authority to require studies in children concerning medical products that will be used in children and under other specific circumstances.

The Public Health Service Act
Section 351 [262] - Licensing requirements for biological products
Section 361 [264] - "The Surgeon General...is authorized to make and enforce such regulations...to prevent the introduction, transmission, or spread of communicable diseases."

FDA Regulations

FDA regulations governing clinical research may be found in the Code of Federal Regulations, Title 21:

- **Part 312:** Investigational New Drug application regulations
- **Part 50:** Protection of human subjects
- **Part 54:** Financial disclosure by clinical investigators
- **Part 56:** Institutional Review Boards

Non-compliance with regulations can have serious consequences including disqualification from further clinical research under FDA oversight.

FDA Guidances

Guidances are developed by the FDA to promote the best practices in the development of a drug or test. By following a guidance, the industry has an accepted method of testing to follow. However, using a method of testing other than in the guidance may be acceptable to the FDA, so a guidance is not like a law or a regulation in that not following the guidance does not carry a legal penalty. The only "penalty" is that the method of testing may not be deemed to be acceptable to the Agency.

The Critical Path to New Medical Products

One of most transforming initiatives of past decade at the FDA is the recognition that the development of new agents has problems that must be addressed by a collective team of FDA, academic and industry representatives. This effort is called the Critical Path Initiative.

The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product. In doing so, the FDA is a "partner" with industry and academia in solving the most challenging problems of product development.

For more information, see:
http://www.fda.gov/oc/initiatives/criticalpath/

Investigators and Sponsors

Understanding your role is critical to your success in comprehending this portion of this course and your success in dealing with FDA regulations relating to your research. Below are brief descriptions of some of the roles in the conduct of clinical research that are addressed by FDA regulations and guidelines.

- **A Sponsor:**
  An individual, company, institution or organization which takes responsibility for the initiation management, and/or financing of a clinical trial is called a sponsor. Most FDA contact is with the sponsor.
- **An Investigator:**
  This is a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called Principal Investigator. Many FDA regulations apply to investigators and these will be discussed later in this section. Also, the NIH may ask the PI to assume sponsor responsibilities.
- **A Sponsor - Investigator:**
  In many NIH clinical research trials, the PI is also the sponsor. In this case, the PI is also responsible for the duties of the sponsor. This situation can raise concerns regarding conflict of interest because of the sponsor's responsibility for the monitoring of the PI.

Investigational New Drug (IND)

When the clinical trial involves investigating unapproved drugs and certain unapproved uses of approved drugs, regulations require a sponsor to submit an Investigational New Drug application--an IND--to the FDA. For investigational devices, an investigational device exemption (IDE) is submitted.

The Contents of an IND Application

The application should include the following types of information with substantial detail to allow evaluation:

- **General Information**
  Cover sheet, table of contents, introductory statement and general investigational plan
- **An Investigator's Brochure**
- **Protocols**
- **Chemistry, Manufacturing and Control (CMC) Information**
  This information may be cross-referenced to another IND or drug master file
- **Pharmacology and Toxicology Information**
  Information regarding animal studies that provides a basis for the design and supports the determination of safety of the proposed human studies. Information regarding the use of this product or a related product in humans, if applicable.
- **Previous Human Experience and Other Relevant Information**

The Review Process for INDs

In brief, the review process for INDs involves the following steps:

1. Contact the FDA prior to submission if you need assistance.
2. Submit the IND for review. FDA IND reviews are conducted by a team of experts in various relevant fields, including medicine, pharmacology, toxicology, chemistry and manufacturing controls, and often statistics.
3. Wait for results of the review. The FDA should notify you of whether your trial has been placed on clinical hold within 30 days. Do not proceed before then.
4. Work with FDA reviewers to resolve any concerns and deficiencies.

If your IND application has certain types of deficiencies that cannot be corrected within the 30 day period, it may be placed on clinical hold and you may not proceed until the deficiencies are addressed and FDA concurs.

Click the NEXT button to learn the types of deficiencies that may lead to clinical hold.

IND: A Clinical Hold

The following can lead to a clinical hold:

- Unreasonable and significant risk
- Investigators assigned to the trial are not qualified
- Investigator's Brochure is misleading, erroneous or incomplete
- Insufficient information to assess the risks
- In Phase 2 or 3 studies, inadequate study design to meet stated objectives

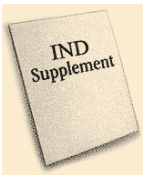
Common reasons for a clinical hold include the following:

- Inadequate product purification, testing or specifications or inadequate data regarding these issues

- Inadequate preclinical safety testing
- Protocol issues such as exclusion criteria, starting dose, dose escalation, patient monitoring

To help avoid a clinical hold, contact the FDA via phone or FDA Web sites well before submitting an IND. You may request a meeting. A sponsor educated in FDA requirements is far less likely to face a clinical hold.

IND Amendments - Protocol Amendments



If certain changes are made to protocols, FDA regulations require the sponsor to submit an IND amendment to the FDA. An amendment is required for the following changes in protocol:

- Changes that affect safety
- Changes that affect scope of Phase 2 or Phase 3 research trials
- Changes that affect scientific quality of Phase 2 or Phase 3 research trials
- A new protocol is added

The following procedures are relevant to IND amendments with protocol amendments:

- Changes to and additions of protocols may be included in the same IND if the drug and indication are the same
- Changes to protocol may be implemented if the IRB has approved them, and the FDA has been notified. There is no 30-day waiting period for FDA review in this case
- However, implementation of new protocol may be placed on clinical hold upon FDA review

Another important responsibility of the sponsor and of investigators is reporting Adverse Experiences. Click the Next button to view AE reporting requirements.

Adverse Experiences

The following organizations, people and documents all play a role in determining adverse experience reporting requirements:

- The FDA and its regulations
- The sponsor
- The IRB
- The protocol
- Your department and institution

You have specific adverse experience reporting requirements as an investigator and additional requirements if you also serve as a sponsor.

The reporting requirements typically depend on the nature of the adverse experience. Three particularly important terms are defined in the following pages:

- Serious
- Unexpected
- Associated with the use of the drug

Serious Adverse Experiences

An Adverse Experience is determined to be serious based upon its impact on the patient. A serious experience results in one of the following:

- Death
- A life threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability / incapacity
- A congenital anomaly (birth defect)
- Experiences that may jeopardize the patient and may require intervention to prevent one of the above outcomes

A severe Adverse Experience is not necessarily serious. Severity describes the level (Grade) of toxicity; however, a “severe” experience may not have a serious impact on the patient. FDA reporting requirements and guidance largely focus on whether an experience was serious. The protocol sometimes establishes additional reporting requirements based on severity.

Unexpected Adverse Experiences

Another relevant factor in reporting Adverse Experience involves whether or not the Adverse Experience was unexpected. By definition, an Adverse Experience is unexpected when the specificity or severity of the experience is not consistent with the current Investigator's Brochure or the risk information described in the general investigational plan.

The regulatory definition of "Unexpected" for an adverse experience depends entirely on whether the type of experience has already been observed with the drug and described appropriately to investigators. It does not depend upon whether the pharmacological properties of the drug or the natural history of the disease leads one to expect it.

Before moving on with the PI's responsibilities as related to the FDA, click the NEXT button to view one last relevant factor involved in reporting Adverse Experiences.

Associated with the use of the drug

- Means there is a **reasonable possibility** that the experience may have been caused by the drug
- Guidance qualifies the definition with "i.e.., The relationship cannot be ruled out."

Investigator Reporting of Adverse Experiences

FDA regulations require an investigator to promptly report to the sponsor any adverse experience that may reasonably be regarded as caused by or probably caused by the drug. Serious adverse experiences must be reported immediately. NIH has specific guidance.

The International Conference for Harmonization (ICH) guideline for good clinical practice advises that all serious adverse experiences should be reported immediately to the sponsor except for those that the protocol or other document (e.g., investigator's brochure) identifies as not needing reporting. Other adverse experiences may be reported as specified in the protocol and in annual progress reports; unless more frequent reporting is required by a regulatory body such as a DSMB, IRB or the FDA.

Sponsors - Adverse Experience Reporting

Below are the sponsor's requirements for reporting Adverse Experiences to the FDA:

- Expedited reports
  - Telephone or facsimile reports
    - If fatal or life threatening
    - Notify the FDA and PIs no later than 7 days from observation
- Written reports
  - Serious, unexpected adverse experience associated with the use of the drug
  - Any findings from tests in laboratory animals that suggest significant risk for human subjects
  - Notify the FDA and PIs no later than 15 days from observation
- Other reports
  - Safety information should be summarized in annual reports

Investigators - Financial Disclosure

Applicants for FDA approval of a drug or biologic are required to submit, as part of their applications, information regarding financial conflicts of interest of investigators in certain trials, largely those establishing efficacy. To meet this requirement, a sponsor may require investigators to provide certain financial information to the sponsor.

A Word About Good Clinical Practice (GCP)

"Good Clinical Practice [is] a standard for design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected." -- ICH Guideline for Good Clinical Practice.

The responsibilities of investigators and sponsors under good clinical practices, including those already discussed, are found in the various sections of the federal regulations cited earlier. The ICH Guideline of Good Clinical Practice, an international document co-authored and endorsed by the FDA, is highly recommended reading for those engaging in clinical trials. It is conveniently organized with a section describing all the responsibilities of an investigator and a section describing all the responsibilities of a sponsor.

Following are some of the responsibilities described in more detail in the ICH Guideline for Good Clinical Practice.

Investigator's Responsibilities

Investigator's Responsibilities under GCP are described throughout this course. The ICH GCP guideline provides a useful description of responsibilities including the following:

- Have appropriate qualifications and resources
- Provide adequate medical care for any adverse experiences
- Provide IRB with appropriate documents and obtain IRB approval
- Comply with the protocol, deviating only with IRB approval, except in case of emergency
- Follow randomization and blinding procedures
- Obtain and document informed consent
- Inform subjects, IRB, sponsor, and the institution of premature termination
- Ensure the appropriate use of the investigational product at the trial site
- Proper handling, storage and recordkeeping of the investigational product at the clinical site

The ICH GCP guideline also describes the investigator's responsibilities for record keeping and reporting - including in the following areas:

- Keep case report forms (CRFs) and allowing access to the IRB, monitors, auditors, and the FDA
- Maintain appropriate trial related documents
- Document financial arrangements with the sponsor
- Provide progress reports to the IRB at least annually
- Report significant changes to the sponsor and IRB
- Report adverse experiences to the sponsor and IRB
- Produce final reports
- Retain the records and reports for 2 years after a marketing application is approved; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been notified

Investigator's Responsibilities, continued:

- 312.60 General Responsibilities of Investigators
- 312.61 Control of the Investigational Drug
- 312.62 Investigator Recordkeeping and Record Retention
- 312.64 Investigator Reports
- 312.66 Assurance of IRB Review
- 312.68 Inspection of Investigator's Records and Reports
- 312.69 Handling of Controlled Substances
- 312.70 Disqualification of a Clinical Investigator

Sometimes an investigator will also assume the role of the sponsor. In other cases, the sponsor may assign some responsibilities to an investigator. Click the Next button to view some of the sponsor's responsibilities.

Sponsor's Responsibilities

The sponsor is the primary party interacting with the FDA, e.g., submitting INDs, protocols, safety reports and annual reports. The following are some of the sponsor's many other responsibilities described in the ICH GCP guideline:

- Maintain quality control and standard operating procedures
- Trial conduct, documentation, reporting, handling data
- Manage the clinical trial, consider establishing a data monitoring committee
- Follow appropriate procedures for handling data and for document retention
- Define trial related functions and allocate responsibilities
- Provide and update an Investigator's Brochure
- Oversee the investigational product
- Quality, characterization, storage, packaging, blinding, supply, disposition, stability, samples and records
- Ensure access to records by monitors, auditors, IRB FDA
- Evaluate safety as trial proceeds - notify investigators, IRB and FDA of important new findings
- Select and train monitors and ensure that the trial is adequately monitored.

Monitoring

Monitoring is one of the important responsibilities of the sponsor under GCP and has a major impact on investigators as well. In this context, monitoring refers not just to the monitoring of accumulating data (as might be done by a Data Monitoring Committee) but to the real-time and almost always on-site monitoring of the conduct of the trial for the purpose of verifying that:

- The rights and well-being of human subjects are protected
- The reported data are accurate, complete and verifiable
- The conduct of the trial complies with the protocol, GCP, and regulations

The terms monitoring and auditing are sometimes used interchangeably. Monitoring, however, is used in FDA regulations and ICH GCP guidance to refer to real-time efforts that not only identify, but also correct and prevent, problems in a trial. Monitors report to the sponsor, but also communicate many findings to the investigator in order to ensure that data errors are corrected and the appropriate actions are taken to prevent recurrence of any observed deviations from the protocol, GCP, or regulations.

DA Guidance Regarding Clinical Trials

The FDA provides valuable guidance for clinical trials such as the following:

- **Product class-specific guidance**
  Examples include gene therapy, medical imaging drugs
- **General clinical trials guidance**
  Examples include GCP, dose-response and choice of controls. Also, the FDA encourages the Sponsor to request an "End of Phase II Meeting" (EOP2) prior to initiating a Phase III trial

- **Therapeutic area guidance**
  Examples include oncology, rheumatoid arthritis
- **Reporting requirements**
  Examples include adverse experience reporting, financial disclosure and annual reporting

Where to Go For Help

A list of pertinent Web sites that will help you with the topic areas discussed in this section, are located on the Main Menu of this training under "Resources for Investigators". Listed below are some of the pertinent sites.

- Official FDA Web site
  http://www.fda.gov
  - Guidance documents
    Biologics: **http://www.fda.gov/cber/guidelines.htm**
    Drugs: **http://www.fda.gov/cder/guidance/index.htm**
    Devices: **http://www.fda.gov/cdrh/guidance.html**
  - Information for clinical investigators
    http://www.fda.gov/cder/about/smallbiz/clinical_investigator.htm
  - IND assistance
    http://www.fda.gov/cber/ind/ind.htm
  - ICH Guideline for Good Clinical Practice
    http://www.ich.org/MediaServer.jser?@_ID=482&@_TYPE=MULTIMEDIA&@_TEMPLATE=616&@_MODE=GLB

FDA Contacts

- **Center for Biologics Evaluation and Research (CBER)**
  Office of Communications, Training and Manufacturers' Assistance
  301-827-1800
- **Center for Devices and Radiological Hazard (CDRH)** IDE and HDE Staff, Office of Device Evaluation 301-594-1190
- **Center for Drugs Evaluation and Research (CDER)**
  Check website for names and numbers

When Should You Talk or Meet With the FDA?

In contacting the FDA, telephone contact and meetings can often avoid lengthy correspondence. Depending on your role, Principal Investigator, sponsor or both, the following situations constitute some appropriate times to meet with the FDA:

- Before you submit your Investigational New Drug Application, especially for first use in humans of novel therapies
- Before you initiate critical efficacy trials, request an EOP2 meeting
- Before you submit an application for marketing

Conclusion

- You are required to adhere to FDA regulations for ethical and safe treatment of human subjects in a clinical research trial
- The ICH Guideline for Good Clinical Practice is a good place to learn more about your responsibilities as an investigator or sponsor
- You can contact the FDA for help

Clinical Investigators and the Mass Media

Based on a presentation by Anne Thomas, M.S., Updated by John Burklow, M.S.

Test Your Knowledge

Before we discuss your relationship, as a Principal Investigator, to the media, test your knowledge with the question below.

You're the principal investigator on a large clinical study of a drug that may control blood sugar levels over a long period of time. Which events in your study are most likely to prompt immediate calls from reporters? Click on the correct answer below.

A. The new drug has no effect on controlling blood sugar levels over a long period.
B. The new drug shows promise for controlling blood sugar levels over a long period.
C. Three of your subjects drop out of the testing for different reasons.
D. Two of your human subjects die while in your study.
E. a, b, and d
F. b and d

Answer

You're the principal investigator on a large clinical study of a drug that may control blood sugar levels over a long period of time. Which events in your study are most likely to prompt immediate calls from reporters?

A. The new drug has no effect on controlling blood sugar levels over a long period.
B. The new drug shows promise for controlling blood sugar levels over a long period.
C. Three of your subjects drop out of the testing for different reasons.
D. Two of your human subjects die while in your study.
E. a, b and d
F. **b and d**

The answer is f.

Reporters would be likely to call if they got word that a new drug showed promise for controlling blood sugar levels over a long period or if two of your human subjects die while in your study.

People clamor for news about new treatments and cures that might impact a large population. Also, deaths in a study raise the investigative instincts of reporters and the interest of the public. Even if the deaths are unrelated to the drug, some reporters will inquire until the cause is determined. While the other occurrences could prompt queries by reporters, they are not as likely to result in immediate calls.

Introduction

Whether it's good news or bad news in medical research, the media wants your story. If your research shows results that could lead to a promising treatment, people want to know about it. The more impact a disease has on society, the more the public wants to know. And they might want to know before you are ready to tell them.

If something bad happens during your research, the media will be on your doorstep too. A patient dies because of an adverse reaction to the therapy you are testing...a human subject suffers because of a protocol that didn't comply with regulations or guidelines...an investigative reporter gets wind of an allegation of conflict of interest... Count on a call or lots of calls from the media.

As an investigator with the NIH, you work for the American public. They have a right to know the good news and the bad. That means that you have to be ready to deal with media inquiries.

Introduction - Why discuss the media in this course?

Good question. The media disseminates information that often brings about needed changes in human subject protection. Many of the major changes, rules and regulations that govern modern clinical practice have occurred as a result of missteps and abuses in history. From the Nazi war crimes to the revelation of Tuskegee and Jesse Gelsinger, the media has played an important role in society's perception of the ethics of clinical research and the necessity of changes.

It's true. Your research with human subjects could end up on the front page or on the evening news, and you will want to know the best way to handle it. Your goal is to be astute, caring and absolutely correct.

In this section, you'll get some advice on how to handle media queries about NIH policy, steps to take when you get the call, what to say and how to say it.

The section also covers embargoes and the Freedom of Information Act.

When you've completed this section, you should have a good feel for what kinds of things to expect from media inquiries and how to best handle them.

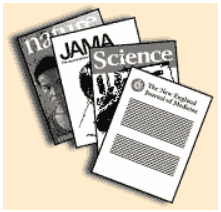
This section, along with the quiz at the end, will take approximately 40 minutes to complete.

What Makes News in Science and Medicine?

Most of the time, media coverage of your clinical trials is desirable and you may wonder why a particular study attracts media attention and yours doesn't.

The following categories describe what draws reporters to cover science and medicine; however, keep in mind that large clinical studies will get more attention than basic laboratory findings, Phase 1 and Phase 2 clinical studies.

Published Science - The Media's Bread and Butter



Scientific studies and research advances that have been published in peer reviewed journals get the most newsprint and television air time by a huge margin. This constitutes the bread and butter of news in science and medicine. Journals such as Science, Nature, New England Journal of Medicine and JAMA dictate, by and large, what is covered by science and medical reporters from week to week.

Novelty - A Little Quirky

As with all news stories, the unusual in science and medicine grabs the attention of the general public. Even folks with little knowledge of science want to hear about things like the cloning of the sheep, Dolly, xenotransplantation, or the administration of vaccines on raw potatoes.

The Unexpected - Who'd a Thunk It?

Think beta-carotene. Most people assumed the study done by NCI and Finnish collaborators would show that beta-carotene helped prevent lung cancer in smokers. Surprise! The study found that beta-carotene not only had no preventive effects, it actually increased the risk. The media jumped on this counterintuitive story.

Or hormone therapy for menopausal women. Everyone thought it was a wonder drug until a large, randomized clinical trial proved otherwise.

Celebrity - The Superman Effect

Think about the impact that the late Christopher Reeve's paralysis had on the national attention to spinal cord injury and research. When Michael J. Fox, the actor, announced his contraction of Parkinson's Disease, public awareness and interest in the disease was heightened. The public, hence the media, want to know about celebrities and their medical problems.

Tragedy and Controversy

One of the most explosive clinical research controversies in recent years is the safety of human gene transfer. The debate was intensified by the death of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania, a highly respected institution. The fallout centered not just on gene therapy, but on researchers all around the country failing to follow NIH guidelines for reporting adverse events. Hundreds of reporters across the nation have jumped on this story.

Impact - By the Millions

Research that has a huge, immediate impact on people gets a great deal of media coverage. For instance, a multi-center clinical trial that reveals the benefit of a new treatment for a common disorder, such as diabetes, would be big news. The immediate impact on people resulting from this type of research is why large clinical studies receive more media attention than basic laboratory findings, Phase I and Phase II clinical studies.

The Media is Simply Great for Science and the NIH

The media lets the public know that research is always moving forward, bringing advances to human health. No other human endeavor, except maybe sports, generates this kind of automatic news peg.

Since the NIH funds much of this multi-center clinical research, we want people to know what we're doing.

Why Reporters Want You

Be willing to talk to reporters.

Reporters tenaciously seek out quotes and experts for many reasons. The next few points will reveal a few of their reasons:

- **Credibility** - Quotes from experts and the people directly involved make the story more credible. For the human gene therapy study at the University of Pennsylvania, print and broadcast reporters followed everyone involved to get a quote--the principal investigator, the FDA official investigating the incident, as well as the father of the young man who died. In reports on human embryonic stem cell research reports always try to include a quote from the NIH director or the head of the NIH Stem Cell Task Force.

- **Clarity and Lively Flavor** - A good quote is usually more interesting than the same information written in a reporter's words and quotes often make the story easier to understand.
- **Tension** - Reporters want interviews because often they find hints of controversy in what you say, and controversy heightens the interest of the public. This fact exemplifies the need for you to think through your words carefully, getting advice when needed, before you speak to a reporter.
- **Limited Time** - news reporters are in a hurry. They often have only a few hours to put a story together and quotes save them from the time it takes to dig up the facts from other sources.

Why You Should Talk to Reporters

Occasionally, a Principal Investigator doesn't want to talk to reporters. He or she would rather have the official spokesperson talk to reporters about their research. This is almost never satisfying to a reporter because the spokesperson is just whoever has been designated to speak on the subject. They aren't viewed as credible as the Principal Investigator because they aren't the expert. The Principal Investigator--**YOU**--are the expert.

You!

NIH spokespeople do speak for the NIH in a crisis or in a story involving a sensitive issue. And they help you prepare to talk with reporters, but we'll discuss more about that later.

The NIH firmly believes that you should talk to reporters, always seeking to be astute, caring and absolutely correct.

You Can Improve the Accuracy of the Story

Many science reporters are smart and very experienced, but they don't know everything about every scientific or medical subject. Even the best science reporters need guidance on emphasis or help in understanding methodology.

You Help Create a Favorable Climate for the NIH

Your input improves public understanding of the importance of medical research and increases support for NIH and research.

You Owe it to the American Taxpayers

The NIH is supported by the taxpayers. Researchers owe it to them to explain their work. The best way to do this is through the mass media. Clinical Investigators especially need to help people understand what an advance in medical research could mean or not mean to their lives. This communication provides an appreciated context to the story for the American people.

Your Words Have Impact - A True Story

When the discovery of the BRCA1 gene was about to be announced in Science Magazine, the embargo was broken a day or two early. We knew the impact of the announcement would be enormous for millions of women who are concerned about breast cancer.

The NIH quickly threw together a press conference and brought the NIEHS scientists who were involved in the discovery to Bethesda. We also had the Director of the Genome Institute and the Director of the National Cancer Institute involved in the press conference, to answer the inevitable questions that would put the discovery into everyday meaning for the public: What does the discovery mean to women? Is there a screening test? When will there be one? Should every woman get the test? Does it relate to all breast cancer?

There were more than 100 reporters present at that press conference and the outcome was highly informative and successful. The scientists provided a consistent and accurate message, saving time and preventing confusion for everyone involved.

Your Words Have Impact - The Process

Reporters may call you directly, without going through your Institute's Communications Office. There is a good way and a not so good way to handle that call from a reporter. Even if the reporter is friendly and wants to do a positive story, you can find yourself in a sand trap if you forget to ask a few key questions. You might end up in the rough if you don't think about how you word your answers.

Although you don't have to get permission from the NIH to talk to a reporter, your laboratory or institute might have a rule requiring clearance. Make sure you know your local policy before you talk to the media. Also, be sure to inform your communications office before you do an interview with major media such as the Washington Post, New York Times, Wall Street Journal or any of the television networks.

If you get a call from a reporter requesting an interview, there are a few things you should routinely do. First, take the reins confidently, and ask a few questions of your own. Click the next button to examine some of the most important questions to ask an inquiring reporter.

You need the answers to the following questions from the reporter before you agree to do anything and be sure to write the answers down.

1. What is your name and phone number?
2. What publication / network / station are you with? (There's a big difference between the *Inquirer* and the *Enquirer*, between *CNN* and *Entertainment Tonight*.)

3. What is your deadline? (This gives you an idea of how much time you have to think about your answer.)
4. What is your angle or story line?
5. Who else are you talking to?
6. What information do you want from me? (Do they just want a background discussion about T cells? Do they want to feature you or just get a quick quote on someone else's work?)

When you have the information, it's a good idea to take a little time to decide if you want to do the interview and to think about what you're going to say. It's also a good idea to get some advice from your institute's Communications Office and to talk to others in your lab or clinic.

To buy yourself some time, you can say something like, "I'd like to think about this a little, first. Can I call you back?" Even if you decline the interview, make sure you return that call quickly, especially if the reporter is on a tight deadline.

As you ponder your answer, keep in mind that reporters are not your pals. They're not cheerleaders for science or your point of view. Most proclaim they are not in the business of educating the public. They are in the business of reporting what THEY think is a news story. Your Communications Officer can help you frame your message in that context.

Your next step should be to consult the Communications Office of your Institute. Your communications officer can help you with the following types of questions:

- Are you the right person to talk to the reporter or is this a hot issue that should be handled by the Communications Office, the director of your institute, the NIH Director or even the DHHS Secretary?
- Should someone outside of the NIH field the questions?
- Is there an NIH position on the subject in question?
- What information about the reporter would be helpful to you, such as the line of questioning they might take?
- How do you say, "No" gracefully, if that's what you decide? The following screen reveals some tips on saying no.

If you decide not to do the interview, decline truthfully and firmly. Below are three common answers; however, not all are the most wise:

Possible Responses:

- **I would love to talk to you, but I've been told not to.** This is not an appropriate answer because an investigative reporter will assume there's a hot story that someone is attempting to hide.
- **I'm not the best person to talk to you about this**. Why don't you contact _____? This is an appropriate answer if it's true. Be sure to give the person you named the courtesy of telling him or her of your referral.
- **It's really too early in the research to have anything firm to say about it**. Again, this is a good answer if it is true. Give the reporter a projected date that she could call back for better information.

On and Off the Record

Beware of a few terms when you're talking to a reporter. Terms of the journalistic trade may not mean what you think they mean. Keep these definitions in mind if you agree to an interview:

Possible Responses:

On and Off the record

1. **On the record**. This means a reporter can quote you directly, using your name and title.
2. **Not for Attribution and On background**. This means reporter, but you are not to be named. You may be identified as an NIH scientist, speak under a condition of anonymity. We recommend that you stay on the record at all times.
3. **Off the record**. This means that a reporter cannot use your information in a story as coming from you; however, he or she can use it in other ways--to get another source to respond to your comment, for example.

Work out the ground rules with the reporter before your interview. You can't take it back after you've said it. And despite these informal rules always speak as if you are *on the record.*

What if You're Misquoted?

Misquotes happen. Even if you follow all of this advice and more, there's a chance your information will be reported in a different light than you anticipated.

If the health message is incorrect and may have an effect on patients or the public, it's important to get the mistake corrected. Call the reporter immediately with the correct information.

If the health message is accurate, but you feel misrepresented, you can call the reporter or the editor or write a letter to the editor. Talk to your institute's communications director and they'll help you decide on a case-by-case basis.

Sometimes the best thing to do is just let it be.

Your Words Have Impact - Another True Story

If you agree to an interview, think about how a patient or family member could interpret your comments on an emotional level? Will your words leave them with no hope? With false hope?

When the New York Times ran an overly positive story about Angiostatin/endostatin, the cancer phone lines at NIH were inundated with calls from people who were ready to show up for clinical trials that weren't even on the drawing board.

Working with a reporter to get an accurate tone in a story can be tedious; however, working with your institute's communications director can help you answer your questions in the best way to both inform the public in terms they will understand and provide a balance.

What the Public Doesn't Know About Science

Surveys show that about 70 percent of Americans say they get their health information from the mass media. That means your words have a great deal of impact.

There are some good basic guidelines to keep in mind when you do an interview with the mass media. The first is that the public - your audience - doesn't know much about how science works. What you say and what they hear might not be the same thing.

- **What You Know**: Research yields new knowledge and raises new questions.
- **What the Public Perceives**: A piece of published science is "The Truth." For example, you might see a study on high fiber diets and cancer as raising more questions than it answers. The public might see it as a definite cancer prevention method.
- **What You Know**: Legitimate scientific differences of opinion exist.
- **What the Public Perceives**: They view differences as confusion. They want the final answer.

Out in Left Field - Unexpected Questions

Now that we've discussed dealing with a reporter's call, understanding what the public hears versus what you say and a few tips for television and radio interviews, it's time to tackle some questions that will come at you from left field. These questions won't necessarily be about your research or even science. The following are "left field" questions that were asked at the BRCA1 gene press conference that was mentioned earlier:

- Who holds the patent?
- What will the test cost the country, and what will it save?
- Will insurance companies cover the cost of the test once it's developed?

People care about these issues today. Even if you don't feel competent to answer them, anticipate that they will arise. Work with your communications office to be prepared for the toughest questions.

When the News Isn't Good

Clinical research has had a bumpy road in the press in the past several years. You can assume that if you or your research encounter certain types of problems, including ethical questions, you will have to deal with media attention. Some types of issues are guaranteed to attract the attention of the mass media.

For instance, numerous headlines were prominent during the investigation of the deaths of five patients in the NIH FIAU. The case stretched out for nearly two years. Finally, the NIH and the clinicians doing the study were exonerated by the NIH Director and the NAS, but the media coverage during the two years was painful for everyone involved - the families of the patients who died, the researchers and the institution.

This tragic story testifies to the fact that horrific events do happen in clinical research. We continue to hold the highest respect for those five patients and sincerest condolences to their family and friends

Other bad news includes scientific misconduct and allegations of conflict of interest, both of which can be extremely painful.

In a scientific misconduct case, "whistle blowers" may need protection. Individuals stand accused and the NIH, as an institution, cannot legally comment at all when legal proceedings or investigations are underway. The intention is not to "hang [the accused] out to dry." The NIH simply cannot legally comment in these types of situations.

A conflict of interest is suspected, to some reporters, when a scientist has any tie to financial interests or to industry. This topic has significant media draw attention as more and more researchers in academia have ties to private industry. As an aside make sure you completely understand the NIH ethics rules.

A Word About Investigative Reporters

Before we move away from the whole idea of doing or not doing interviews, take a little time to consider a special breed of reporter: Investigative Reporters. They are likely to be the reporters who uncover the bad news we' ve just discussed. Keep the following in mind about these tenacious reporters:

1. They have more time than the average reporter who has a daily deadline to file.
2. They are most interested in irregularities, violations and / or misconduct.
3. They try to cultivate "whistle blowers" or unconventional sources.
4. They will use the Freedom of Information Act to obtain documents, whereas a daily reporter wouldn' t generally do this.

If you determine the reporter interested in interviewing you is an investigative reporter, contact your institution' s communication officer. They, in turn, will call the reporter and decide how to proceed.

The Freedom of Information Act (FOIA)

The Freedom of Information Act makes documents available to anyone, whether or not they are a citizen and whether or not we think they have a need to know. You cannot withhold documents because they make us look bad or because they could be misinterpreted by the public. There are nine exemptions in the Freedom of Information Act that permit the NIH to withhold documents. The two exemptions that are most often used are the following:

1. Invasion of personal privacy, such as release of medical records
2. Commercial or financial information

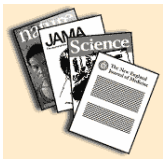
The following are documents that are available to anyone at any time under FOIA:

- Approved research protocols
- Minutes of NIH Institution Review Boards, with some possible deletions
- Your e-mail messages
- Your computer files
- Document drafts

Under FOIA, it doesn't matter if you stamp a document "Confidential" or not. Each request is considered anew. Each Institute has a FOIA officer to help you with requests. You will be involved in the process, but only one person at NIH - an attorney in the Office of Communications - has the authority to deny documents under the Freedom of Information Act.

Take precautions. How would your documentation look if it were released to someone who wants to sue you or an investigative reporter who thinks you are the villain of the story?

Embargoes



An embargo is an agreement between a scientific journal and reporters. It designates the time frame in which a story may be released. In other words, embargoes are dates established by scientific journals that prevent the release of stories before a certain date.

For example, the December issue of the NEJM hit the newsstands on the 14th. Copies were sent to the press and NIH several days ahead of that, but we cannot release any information on the stories until the evening of December 13. Likewise, if you are an author of an embargoed story, you must remind reporters that you are speaking under an embargo.

Also, refrain from talking to non-journalists about an embargoed article because they are not held to the same restraints as reporters. There is a danger in science and medicine that talking about a pending study result could start "insider trading" and stimulate an investigation by the Security and Exchange Commission - if the stock market showed unusual movement, for example.

Sometimes an ambitious reporter will jump the gun and break a story before the embargo. What happens then?

- The journal may lift the embargo.
- News stories may run ahead of schedule
- You may be permitted to proceed immediately with interviews

Whatever happens, you should contact your institute's communications officer for instructions.

Before moving on, it's important to note that the future of embargoes is uncertain. With more clinical papers having many authors, with fierce competition from reporters, with people posting their data on the Internet, and with the economic importance of clinical advances, embargoes are unlikely to stand.

The Inglefinger Rule

The Inglefinger Rule, named after a former editor of the NEJM, was levied in the 60's to control early release of NEJM article information. The Inglefinger Rule has succeeded in intimidating some scientists to the point that they feel uncomfortable giving media interviews - even delivering abstracts at a medical meeting--for fear they won't get published.

The rules have since been clarified by NEJM and JAMA and are more liberal. You can talk freely at meetings and still get published. You can talk to reporters about what you presented at meetings, but it is probably not a good idea to go beyond what you presented in public sessions or to hand out the details of your data before publication. Also, **never give out your manuscript to a reporter**.

Events do infrequently occur that make both embargoes and The Ingelfinger Rule moot.

Clinical Alerts

In the 1990's, journals moderated their views about releasing details concerning certain studies prior to publication, in part persuaded by the NIH and in recognition of the public's need to know. These cases, which remain rare, are wrapped up in the term Clinical Alerts.

Some prominent journals now allow agencies such as the NIH and CDC to hold press conferences prior to publication when the data are very compelling and have a very immediate impact on public health. In short, if lives can be saved by disseminating the information immediately, then it is allowed without jeopardizing publication.

One example would be when a data safety monitoring board, in looking at a study, sees a clear advantage or disadvantage in one arm of the study and recommends to the funding agency that the study be discontinued for ethical reasons. Then the NIH, as an institution, may find that we cannot ethically keep the information from the wider public.

When to Contact Your Institute's Communications Director

Throughout this presentation, several circumstances have been discussed that call for assistance from your institute's communications director. The following list condenses those circumstances in which it would be appropriate for you to contact your communications director:

- When you get a request from a reporter for an interview. This isn't required, but it's a good idea for your own comfort level.
- Any time you are doing an interview with a **major** newspaper, magazine or TV network.
- To get help on how to phrase answers for the public.
- To do a dry run for a TV or radio.
- To learn what NIH policy is on a matter.
- When you're concerned about an investigative reporter who wants to talk to you.
- If you have a question about embargoes.

Conclusion

As a clinical researcher you may find yourself in demand for media interviews. Remembering these key points will help you successfully deal with the media:

- People want to hear science and medical news.
- As a government institution, we are obligated to inform the public about our work.
- Understand that bad news or an ethically questionable problem draws media attention.
- The NIH encourages you to talk with reporters. It adds credibility and reflects well on the NIH.
- If you get a call from a reporter, get the information you need before agreeing to the interview.
- Use plain language in explaining your work for the general public.
- Assume everything is on the record.
- Be aware of media issues, such as embargoes, that are unique to scientists.
- Contact your institute's communications officer for assistance.

When you're finished exploring these questions, click the Next button below to proceed to the test questions for this section. When you've answered the questions for this section, click the Submit button.

CLINILABS
CLINICAL DRUG DEVELOPMENT

21 CFR Part 11

Electronic Records; Electronic Signatures

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Training Objectives

- Review 21 CFR Part 11 Requirements
- Review requirements in FDA Guidance document "Computerized Systems Used in Clinical Investigations"

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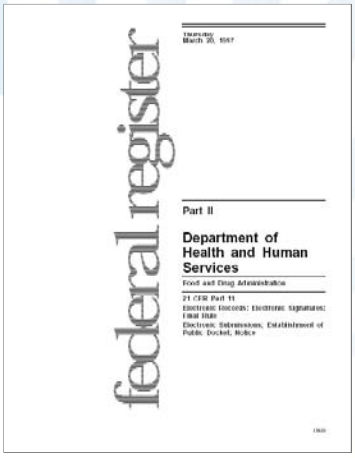
CLINICAL DRUG DEVELOPMENT

21 CFR Part 11 Overview



- Final Rule Published in 1997
- 1999 – Computerized Systems Used in Clinical Trials (CSUCT)
- 2003 – "Scope and Application" Guidance

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21 CFR Part 11 defines an Electronic Record as…

…any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

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21 CFR Part 11 Overview

Part 11 allows ...

=

Electronic Records equivalent to Paper Records

Approved by: John Doe
09:19:2006; 13:15

= John Doe 9/19/2006

Electronic Signatures equivalent to Handwritten Signatures

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21 CFR Part 11 Overview

… but only if Part 11 Requirements are met.

- Electronic Record Requirements
  - Validation
  - Data Integrity
  - Security - Authorized Users, Device Checks
  - Audit Trails

CLINILABS
CLINICAL DRUG DEVELOPMENT

21 CFR Part 11 Overview

… but only if Part 11 Requirements are met.

- Electronic Signature Requirements
  - Signature Manifestations
  - Signature / Record Linking
  - Identification Code and Password Controls
  - Procedural Controls and Policies

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Computerized Systems Used in Clinical Investigations

History

- 1999: Computerized Systems Used in Clinical Trials
- 2004: Draft Computerized Systems Used in Clinical Trials Guidance
- May 2007: Final Guidance Published

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Computerized Systems Used in Clinical Investigations

Background

- Increasing use of computerized systems in clinical trials
- FDA's acceptance of clinical data depends on ability to verify the quality & integrity of the data.
- E-Source records must meet same data quality elements as paper records

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Computerized Systems Used in Clinical Investigations

Scope

- Data recorded on hardcopy and later entered into computerized system
- Direct entry of data into a computerized system
- Data automatically recorded into a computerized system

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Terms

- Source Data
  - All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Source Documents
  - Original documents, data, and records.

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Examples of Source Documents

- Hospital Records
- Clinical & Office Charts
- Laboratory Notes
- Memoranda
- Subject Diaries / Evaluation Checklists
- Pharmacy Dispensing Records
- Recorded data from Automated Instruments
- Copies or transcriptions certified as being accurate and complete
- Microfiches
- Photographic Negatives
- Microfilm or magnetic media
- X-rays
- Subject files

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Terms

- **Original Data**
  - Those values that represent the first recording of study data. FDA is allowing original documents and the original data recorded on those documents to be replaced by copies provided the copies are identical and have been verified as such (see Compliance Policy Guide 7150.13).

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CPG 7150.13

- Acceptability of Microfiche or Microfilm
  - All records must be available for review and copying by FDA in a reasonable time.
  - Equipment must be available for viewing / copying records.
  - Copy must be true and accurate of the original.

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Computerized Systems Used in Clinical Investigations

- Study Protocols
  - Protocols should identify steps where computer systems will be used for source data
  - Computer systems should be designed to:
    - Meet protocol requirements
    - Prevent data errors

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Computerized Systems Used in Clinical Investigations

SOPs for Use of Computerized Systems

- Note: They must be available to site at all times

Recommended List of SOPs

- System Setup / Installation
- User Manual
- Validation and Testing
- Data Collection and Handling
- System Maintenance
- Security
- Change Control
- Backup, Recovery & Contingency
- Alternate Recording Methods
- Computer User Training
- Roles/Responsibilities for Computer Systems

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Computerized Systems Used in Clinical Investigations

- Source Documentation / Retention
  - Clinical investigator must retain source documents
  - When source documents are transmitted to sponsor, copies should be maintained at other location (e.g., site or third party)
  - Copies should be made at time of data entry and preserved in appropriate format.

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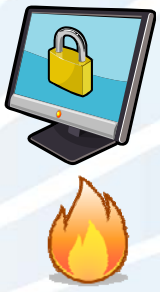
Computerized Systems Used in Clinical Investigations

- Security
  - Access must be limited to authorized individuals
  - Each user assigned individual account
  - Limit # of log-in attempts
  - Record unauthorized access log-in attempts
  - Prohibit password sharing
  - Log off workstation if not in use
  - Virus protection
  - Maintain record of users, along with access rights



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Computerized Systems Used in Clinical Investigations

- Audit Trails
  - Necessary for reconstruction of study conduct and source data collection
  - Based on risk assessment computer generated audit trails should include:
    - Date/time
    - Person Making Change
    - Reason for Change
    - Original Entry

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Computerized Systems Used in Clinical Investigations

- Date/Time Stamps
  - Controls need to assure date/time stamps are correct
  - Only authorized personnel can change
  - All changes should be documented
  - Synchronization to time standard
  - Time zone handling convention should be documented

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Computerized Systems Used in Clinical Investigations

- Other Controls
  - For direct data entry, include controls to assure consistent system use and out of range data
  - Hardware and software should be identified and available for FDA inspection
  - Backup and restore procedures

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Computerized Systems Used in Clinical Investigations

- Other controls
  - Change control
    - Software upgrades
    - Security and performance patches
    - Equipment
    - Instrumentation
    - Component replacement
  - Training for persons who develop, maintain or use computerized system

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Summary

- Review 21 CFR Part 11 Requirements pertaining to Electronic Records and Electronic Signatures
- Review FDA Guidance on Computerized Systems Used in Clinical Investigations

CLINILABS
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Good Clinical Practices

Basic Principles and Considerations

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Training Objectives

- Review the principles and elements of Good Clinical Practices (GCP)
- Discuss FDA and International Conference on Harmonisation (ICH) GCP requirements and their relationship to the Declaration of Helsinki
- Address informed consent
- Define roles and responsibilities for:
  - Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
  - Investigator
  - Sponsor

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Introduction

- Good Clinical Practice
  - "…an ethical and scientific standard for all aspects of clinical research involving human subjects. This crucial standard strengthens public assurance that, with compliance, the legal rights, health, safety, and privacy of human subjects are the best interests of clinical trial researchers."

ICH E-6: Good Clinical Practice Consolidated Guidance

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Introduction

- GCP and safe clinical research go hand in hand
- The ICH, FDA, and The World Medical Association (WMA) provide the foundations for GCPs
- GCP concepts began with Nuremberg Code and The Declaration of Helsinki

CLINILABS
CLINICAL DRUG DEVELOPMENT

Introduction

- GCP and the protection of human subjects are the most important considerations when designing and conducting clinical research investigations
- GCPs apply to all aspects of clinical research
- GCP and safe clinical research go hand in hand
- The ICH, FDA, and The World Medical Association (WMA) provide the foundations for GCPs
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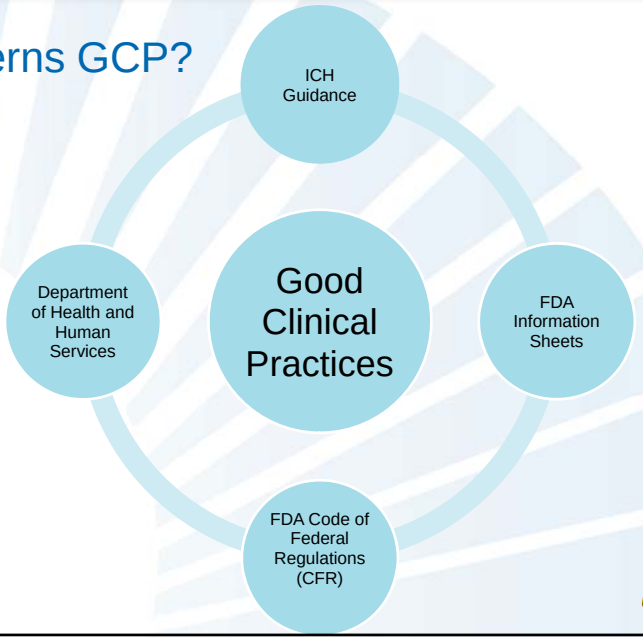
What Governs GCP?

Several different bodies and their standards apply to GCPs



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Introduction

GCPs are influenced by three organizations:

- The WMA through the Declaration of Helsinki
- ICH through Guidance (i.e. E-6) documents and other documents
- U.S. FDA through the Code of Federal Regulations (CFR), Information Sheets, and Guidance documents

CLINILABS
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Introduction

- ICH E-6: Guidance for Industry: Good Clinical Practice: Consolidated Guidance
  - Provides a unified means for conduct of clinical studies between the European Union (EU), Japan, and the US
  - Not legally enforceable → "Guidance"
  - Main industry standard for GCP

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Introduction

- FDA Code of Federal Regulations (CFR)
  - Provides regulations for GCP in the US
  - Enforceable by US law
  - Applicable regulations to GCP:
    - Part 50: Protection of Human Subjects
    - Part 54: Financial Disclosure by Clinical Investigators
    - Part 56: Institutional Review Boards
    - Part 312: Investigational New Drug Application
- FDA Information Sheets
  - Current guidance on protection of human subjects of research.
  - Help IRBs, clinical investigators, and sponsors with legal responsibilities

CLINILABS
CLINICAL DRUG DEVELOPMENT

Introduction

- GCP and the protection of human subjects are the most important consideration when designing and conducting clinical research investigations
- GCPs apply to all aspects of clinical research

CLINILABS
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The Nuremberg Code*

- The voluntary consent of the human subject is essential.
- "The experiment should yield fruitful results of the good of society and not random and unnecessary in nature."
- The experiment should be designed and based on the results of animal experimentation, a knowledge of the disease that the anticipated results will justify the performance of the experiment.

* Established from Trials of War Criminals before the Nuremberg Military Tribunal, 1946 - 1949

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The Nuremberg Code (cont'd)

- The experiment should be conducted to avoid all unnecessary physical and mental suffering.
- No experiment should be conducted if there is reason to believe death or disabling injury will occur.
- The degree of risk should never exceed the importance of the problem solved by the experiment.
- Proper preparations should be made to protect the experimental subject against injury or death.

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The Nuremberg Code (cont'd)

- The experiment should be conducted by scientifically qualified persons.
- The subject should be at liberty to bring the experiment to an end.
- The scientist in charge must be prepared to terminate the experiment if it is determined that continuation is likely to result in injury or death.

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Declaration of Helsinki

- Adopted in 1964 by the World Medical Assembly (WMA)
- Statement of ethical principles to provide guidance to physicians in medical research involving human subjects
- It is the duty of the physician to promote and safeguard the health of the people.
- "The health of my patient will be my first consideration."
- "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

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Definitions

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
  - An independent body constituted of medical, scientific, and nonscientific members,
  - Responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects
  - Review, approve, and provide continuing review of trials, protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
- Protocol
  - Describes the objective(s), design, methodology, statistical considerations, and organization of a trial
  - Background and rationale for the trial (optional)

CLINILABS
CLINICAL DRUG DEVELOPMENT

Definitions

- Data and Safety Monitoring Board (DSMB)
  - An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.
- Informed Consent:
  - A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).

CLINILABS
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Definitions

- Blinding/masking
  - A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).
- Randomization
  - The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

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Principles of GCP

- Benefits of research should outweigh the risk to subjects
- Welfare, legal rights, and safety of the subject are the main priority of research
- Adequate information about the investigational product should support the trial
- Trial needs to be reviewed by the IRB/IEC with favorable opinion and needs to be carried out in the same manner
- Qualified physician should administer any medical care to subjects

CLINILABS
CLINICAL DRUG DEVELOPMENT

Principles of GCP (cont'd)

- Only individuals qualified to perform trial-related duties should participate in a trial
- Obtain Informed Consent before proceeding with trial
- Document the conduct of the trial to allow reconstruction of trial activities
- The Subject's Private Health Information should be maintained
- Follow Good Manufacturing Practices for the manufacture of the Investigational Product
- Quality Systems need to be implemented prior to conducting the study

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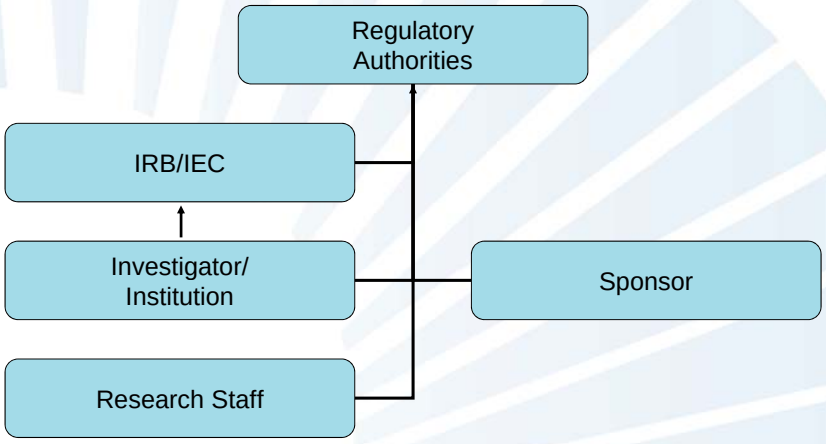
Reporting Structure



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Composition of IRB/IEC

- The following criteria should be considered in choosing the IRB/IEC:
  - A minimum of five members
  - One member of a nonscientific interest
  - One member who is unrelated to the clinical investigation
- Only members who are independent of the investigator or sponsor should give an opinion or vote on trial-related matter

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IRB/IEC Responsibilities

- Protect subjects' rights
- Obtain/Review all documentation
- Periodic reviews of trial and expedited reporting
- Evaluate completeness of information for clinical investigation
- Evaluate nontherapeutic trials with ethics
- Determine protocol for emergency situations
- Evaluate compensation plan and monitor
- Review Investigator Brochure (IB)

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Functions of IRB/IEC

- Meetings should be announced and all activities or minutes should be clearly recorded
- Present decisions at announced meetings, only when a quorum of members is present
- No one outside the IRB/IEC review and discussion should vote or express their opinion
- An IRB/IEC member may consult an expert to provide support for special areas

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IRB/IEC Procedures

- Composition, function, and responsibilities of IRB/IEC should be documented in writing for every trial
- Review clinical investigations:
  - Prior to initiation of study in a reasonable time frame
  - Periodically to assess progress and GCP compliance
  - To approve/update any minor changes to study before study continues

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IRB/IEC Procedures (cont'd)

- Announce that IRB/IEC written approval of the study is essential prior to initiation of study
- Notify trial staff that deviations or changes to study must be reported immediately to IRB/IEC
- Maintain the CVs of all IRB members

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Investigator Responsibilities

- All investigators should be adequately qualified, educated and trained
- Should have enough experience to perform trial-related duties
- Maintain a list of qualifications of all trial-related staff
- Familiarize themselves and all staff with protocol, regulations, and any other information for trial

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Adequate Resources for Investigator

- The investigator should be able to assert the following:
  - Adequate interest by potential subjects for recruitment
  - Sufficient time to complete trial within a pre-determined period
  - Adequate number of qualified staff and facilities
  - Persons involved in study are well-informed of all aspects of the trial

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Adequate Resources for Investigator (cont'd)

- Investigator is also responsible for obtaining informed consent from the subjects
  - Must adhere to regulatory requirements referred to in 21 CFR Part 50, ICH E6 Guidance, and the Declaration of Helsinki
  - Update documents as necessary

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Form FDA 1572

- Contract between FDA and the Investigator
- Includes logistics such as names and addresses
- Section 9
  - Commitments of the Investigator

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Medical Care of Trial Subjects by Investigators

- Overall medical care of subjects is the responsibility of the IRB/IEC
- Any trial-related medical matters should be handled by an investigator- or subinvestigator-physician
- Monitor adverse events subjects during and after the trial
- Make a reasonable effort to determine reason for premature withdrawal from a study by a subject
- Inform the subject's physician about participation in the trial

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Communication with IRB/IEC

- Investigator/Institution is required to:
  - Submit current Investigator Brochure (IB)
  - Obtain written approval/favorable opinion
  - Submit all documentation to the IRB/IEC
  - Follow pre-approved protocol
- If subject is at risk and there is not sufficient time (emergency), investigator:
  - May make a decision without IRB approval
  - Submit a detailed written report of events to IRB/IEC and/or regulatory authorities

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Emergency Communication with IRB/IEC

- If subject is at risk and there is not sufficient time, investigator:
  - May make a decision without IRB approval
  - Is required to submit a detailed written report of events to IRB/IEC and/or regulatory authorities with a full explanation of the issue

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Compliance with Protocol

- Always conduct trial according to pre-approved protocol
  - Should be signed by sponsor and investigator
- No deviations without prior agreement with sponsor and approval from IRB, unless:
  - Patient's health or safety is jeopardized
  - Minor administrative or logistical changes
- Any deviations should be thoroughly documented by investigator or other pre-qualified individual

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Compliance with Protocol

- When prior approval is not possible, deviations/amendments need to be presented to:
  - IRB
  - Sponsor
  - Regulatory authorities
- Investigational Product
  - Responsibility rests with investigator or their designee
  - Maintain all records (i.e. shipping logs, dates, etc)
  - Store according to sponsor's requirements
  - Ensure proper product use by subjects

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Informed Consent of Trial Subjects

- Adhere to all applicable regulatory requirements
- No coercion
  - i.e. Peer pressure, bribery
- Obtain IRB-approval on any updates to ICF
- State legal rights of subject, investigator, sponsor, IRB
- Provide all trial information in comprehensible language
- Provide time to understand materials and consent
- Documents need to be signed by the subject

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Informed Consent Document

- Must contain elements of informed consent relevant to your clinical trial
- Protocol title
- Version date of the consent form
- Page numbers
- Participant signature line

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Randomization Procedures and Unblinding

- Trial-specific unblinding procedures should be followed by the investigator:
  - Assess the necessity of unblinding first
  - Only in accordance with protocol
  - Document reason for premature unblinding and report it to sponsor

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Trial Design: Measurements

- Safety
- Efficacy
- Primary endpoint/objective
- Secondary endpoint/objective

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Trial Design: Blind or Open

- Blind
  - Single Blind
  - Double Blind
- Open or open-label
  - All parties know the identity of the subject's treatment

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Trial Design: Randomization

- Treatment assigned by some element of chance.
- Treatment groups may be stratified (divided) into different sub-groups based on characteristics such as age, gender, and race.

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Trial Design: Sample Size

An adequate sample includes a population large enough to make generalizations from the data.

- Statisticians will help answer question

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Stopping the Clinical Trial

- Development can be stopped at any time
  - Safety
  - Efficacy
  - Business Reasons/$$$
- Clinical trial can be halted at one site or all
- Clinical trial can be halted by the PI, IRB/IEC, Sponsor, or the CRO

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Sponsor Responsibilities

- Implement and maintain **Quality Control Systems**
- Conduct periodic **audits/reviews** of trial
- Maintain a complete and accurate set of **SOPs**
- Assure **compliance with protocol**
- Document any **duties given to a CRO**, if applicable
- Assign **medical expertise** when necessary

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Sponsor Responsibilities (cont'd)

- Select only **qualified individuals** to conduct study
- Assign **roles and responsibilities** prior to start of trial
- Document the **payment/compensation plan**
- Submit **applications** to regulatory authorities
- **Review/Favorable opinion** from IRB/IEC
- **Review all information** for the Investigational Product
  - Must be phase specific

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Sponsor Responsibilities (cont'd)

- Efficacy, Safety Data, Storage, Packaging
- Only allow direct access to source documents according to study protocol
- Follow the procedure/protocol for reporting adverse and serious adverse events
- Select qualified monitors who can communicate between investigator and sponsor

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Summary

- Ethical and scientific standards should govern clinical research
- Conduct of clinical trials is dictated by:
  - The Declaration of Helsinki
  - ICH Guidance
  - FDA CFRs, Information Sheets, and Guidance
- GCP Basics
  - To protect the human subject
  - Maintain the integrity of the study
  - Completely and accurately document everything
  - Safely design and adequately conduct the trial

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Summary (cont'd)

- Submit all essential documents to IRB, sponsor, and all appropriate regulatory agencies
- All study-related staff should be educated and qualified to conduct the study

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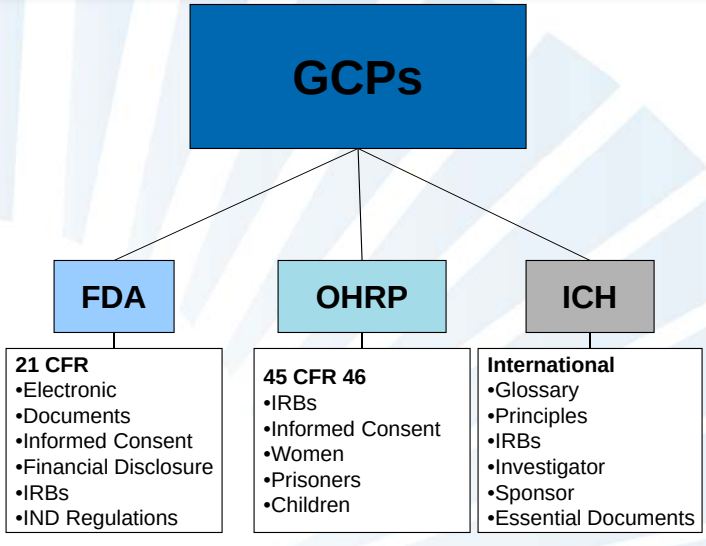

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Best Ways to Comply with GCP

- Research staff need to be qualified
- Always obtain informed consent with any perspective subject
- **Documentation!**
- **Confidentiality!**
- Ensure proper handling and storage of investigational products
- Implement and enforce quality systems

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Informed Consent

Principles and Regulatory Requirements

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Expectations

- Understanding principles and procedures
- Basic elements
- Who's responsible for what?
- What to do in case of emergency

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Not-So-Informed Consent

- Nuremberg Code
  - Trials of War Criminals, Nuremberg Military Tribunal, 1946 - 1949
  - Voluntary consent
- Declaration of Helsinki
  - World Medical Assembly (WMA) 1964
    - Ethical principles to provide guidance to physicians in medical research
    - Duty to promote and safeguard health
- ICH Guidance E-6:Good Clinical Practices
  - Ethical principles for treatment of subjects

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Main Goals of Informed Consent

- To inform participants about research
- To allow participants to evaluate whether they want to take part in the research and if the risks are acceptable to them
- To document the consent process
- Use ethical principles with patients

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Building Relationships with Subjects

- **Establish**
  - Preferences/expectations
  - Screening/anticipating difficulties
  - Developing mutual confidence/respect
- **Structure**
  - More control for subject
- **Enhance**
  - Realistic expectations
  - Enhance cooperation and participation in care

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Terms

- Legally Authorized Representative
  - An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure involved in the research.

    21 CFR 50.3(l)
- IRB – Institutional Review Board
  - A group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such clinical research.

    21 CFR 50.3(i)

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Terms

- Test Article
  - Any drug (including a biological product for human use), medical device for human use,…or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

    21 CFR 50.3(j)
- Minimal Risk
  - The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

    21 CFR 50.3(k)

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Terms

- Permission
  - The agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be in compliance with 21 CFR 50, Subpart B, Informed Consent of Human Subjects.

    21 CFR 50.3(r)
- Assent
  - A child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as consent.

    21 CFR 50.3(n)
- Children
  - Persons who have not attained the legal age for consent to treatments or procedures involved in a clinical investigation.

    21 CFR 50.3(o)

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21 CFR 50.20
General Requirements for Informed Consent

- No subjects may be involved in a clinical investigation without a signed, legally effective, informed consent form.
- Sufficient time should be provided for subject to consider consent.
- The possibility of coercion or undue influence should be minimized.

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21 CFR 50.20
General Requirements for Informed Consent

- Informed consent language should be understandable.
- Informed consent cannot include language which waives the subject's legal rights.
- Informed consent cannot release sponsor, investigator, or institution from liability for negligence.

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21 CFR 50.25
Elements of Informed Consent

- **The following information should always be included in the informed consent form:**
  - Study **involves research**, including the **purpose** of the research.
  - **Expected time frame**
  - Description of **procedures**
  - Statement that **procedures are experimental**.
  - **Forseeable risks or benefits**
  - **Alternative procedures** or **treatments**
    - "You may receive drug x outside of this study."

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21 CFR 50.25
Elements of Informed Consent

- The following information should **also be included in the informed consent form:**
  - Confidentiality
  - Compensation
  - Available medical treatments
  - Contact information
  - Participation is voluntary
  - Participation can be discontinued at any time

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21 CFR 50.25
Elements of Informed Consent

- **Additional Elements** of Informed Consent may include:
  - **Potential risks** which are **unforeseeable**
  - **Termination** of participation at the investigator's discretion
  - **Additional costs**, if any, that the subject may incur
  - **Consequences** of subject's decision to prematurely withdraw
  - **New findings** identified during research will be provided to subject
  - **Number of subjects** in study

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21 CFR 50.27
Documentation of Informed Consent

- When obtaining informed consent:
  - Form must be **approved by the IRB**, prior to use.
  - **Signed and dated** by the subject or the subject's legally authorized representative.
  - Give a **copy** to the subject.
  - A **Short Form** written consent document (for oral presentation)
    - The IRB will approve a written summary of what is presented.
    - A witness is required who will sign both the Short Form and summary.

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Tips for Writing Informed Consent Forms

- 8th grade reading level:
  - Small words
  - Short sentences
  - Action verbs
- Layman's terms
- Be direct
  - i.e. using "You"

"We'll widen the clogged artery by inserting a balloon."

Do Not Try to Confuse the Subject!

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21 CFR 50.23
Exceptions from General Requirements

- Test articles may be used without informed consent, but:
  - The investigator and a physician not involved in the study must certify in writing that:
    - **Life threatening situation; and**
    - **Inability to communicate with subject; and**
    - **Insufficient time; and**
    - **No alternative method or therapy.**

Each factor must apply

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21 CFR 50.23
Exceptions from General Requirements

- Immediate use of test article is acceptable without written certification if investigator determines subject's life is in danger.
  - Independent physician must provide written evaluation and review within 5 working days after use of test article.
- Written certification or evaluation must be submitted to IRB within 5 working days after use of test article.

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21 CFR 50.24
Exceptions for Emergency Research

- IRB may approve the clinical investigation without requiring informed consent if:
  - Life-threatening situation
  - Alternative methods are not available
  - Scientific research is needed to determine safety and effectiveness of an intervention
  - Medical condition

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21 CFR 50.24
Exceptions for Emergency Research

- IRB may approve the clinical investigation without requiring Informed Consent if (continued):
  - The IRB has approved the Informed Consent process and documentation.
  - Additional protections of subjects are provided
    - (i.e. independent data monitoring committee)
  - Will contact legally authorized representative within a specified time frame

Documentation of activity is necessary!

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21 CFR 50.24
Exceptions for Emergency Research

- IRB may approve the clinical investigation without requiring informed consent if (continued):
  - Intervention must be administered
  - Subjects cannot be prospectively identified
  - Direct benefit to the subject
  - Trial cannot be conducted without the waiver

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Past exceptions to informed consent requirement

- Emergency
- Mandatory donation
- Threat to community
- Dependents
- Contagious disease
- Criminal law enforcement
- Dangerousness
- Pregnancy
- Civil law discovery
- Impaired capacity
- Prison management
- Commitment
- Disorientation
- Preservation of life
- Life of Others
- Prevention of suicide

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21 CFR 50 Subpart D
Additional Safeguards for Children
Informed Consent Requirements

- **Both** parents must give their permission
- IRB will determine how **assent**, if required, must be documented.

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Summary

- Always obtain informed consent from a perspective subject.
- 21 CFR 50.23 and 21 CFR 50.24 – Exemptions
- 21 CFR Part 50.25 – Basic Elements
- Update ICF throughout the clinical investigation
- 21 CFR 50, Subpart D – Special Requirements for Children

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Serious Adverse Events Training

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Training Objectives

- Purpose of reporting AEs
- Define pre-existing conditions
- Severity vs. Seriousness of AEs
- Assessment of relatedness to investigational product
- Define Unanticipated Problem (UP)
- Investigator responsibilities
- Sponsor Responsibilities

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Adverse Event (AE) *ICH Guidance E6 1.2*

- Any untoward/unfavorable medical occurrence in a study subject

- that develops or worsens during/ after administration of Investigational Product (i.e. temporal relationship)

- but may not necessarily have a causal relationship with this treatment

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What are Adverse Events?

Unfavorable Changes in Baseline Health	Example
Physical signs and symptoms	Developing a rash after receiving a test article
Abnormal laboratory values	White blood cell count value that is out of "normal" range
Changes in vital signs, physical examinations, or electrocardiogram	Blood pressure changes from being in the "normal" range to being in the "high" range
An increase in the frequency or intensity of a pre-existing condition	Migraine headaches that increase in frequency from once a month to once a week
Complications as a result of a surgery or procedure	Infection status post an appendectomy

Slide 3

MSOffice1 Redesign with text boxes and arrows, need to reword slightly
, 12/31/2007

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Definitions

- **Serious Adverse Event (SAE)**
  - Is a **congenital anomaly** or birth defect
  - Is any other **important medical events**, based upon appropriate medical judgment, that may jeopardize the subject or may require medical or surgical intervention to prevent or avert one of the outcomes listed above

Good Clinical Practices.
E6, 1.50. ICH.

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Definitions

- **Adverse Drug Reaction (ADR)**
  - "In the *pre-approval clinical experience* with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:
    - All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions."

Clinical Safety Data Management: Definitions for
Expedited Reporting E2A, II. A.2. Adverse Drug Reaction. ICH.

- **Expected Adverse Drug Reaction –**
  - Any adverse reaction whose nature and intensity are consistent with that documented in the Investigator Brochure (IB) or the general investigational plan

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Definitions

- **Baseline -**
  - Protocol designated time point from which changes in status are measured.
  - Depends on the study design, but should be the same for all subjects in the study.
    - **Ex.**
      - **Baseline - Subject experiences mild pain in his right knee, but no other ailments**
      - **Test article is administered – Subject experiences severe pain and cannot walk on right leg**
      - **There has been a significant decrease from baseline health**

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Definitions

- **Life-threatening**
  - An event where the subject actually needs intensive therapy or rehabilitation or medical care to resolve the reaction
  - Subject is at risk of death at the time of the event
    - Does not consider something that could have happened and would have put the subject near death as life-threatening
    - Ex. Life-threatening: Subject experiences septicemia after administration of test article
- **Unexpected Adverse Drug Reaction**
  - "An adverse reaction, the nature or severity of which is not consistent with the applicable product information."

Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A.II. A. 1.60.ICH.

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Definitions

- **Pre-existing condition**
  - Any chronic, recurring condition identified prior to enrollment, whether present at enrollment or not.
    - Examples: lymphoma, eczema
  - To ensure no pre-existing condition is missed:
    - Do a thorough screening to assess and document pre-existing conditions
    - Document any concomitant medications at baseline condition
    - **Note: Pre-existing condition is not an AE unless the condition becomes more severe or frequent due to the investigational product (IP)**

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Why are Adverse Events Collected?

- To protect the safety of patients involved in clinical trials, by:
  - Appropriate modification of study protocols
  - Improvement in study design or procedures
  - Termination of subject's involvement or trial
  - Improve understanding of the overall safety profile of the product
  - Evaluate the benefits and risks of a drug
  - Provide information for the package insert if a drug is marketed
  - Comply with regulatory requirements

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When Does An Adverse Event Become Serious?

- Results in Death
- Life threatening, i.e. subject is at immediate risk of death from the reaction as it occurred
- In-patient hospitalization or prolongation of existing hospitalization
- Disability or incapacity
- Congenital anomaly or birth defect
- Any medical event that puts the subject at risk or requires medical or surgical intervention to prevent or avert one of the previously listed events

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Determining Severity of an Event

- **Characteristics of Severe:**
  - Marked limitation in activity
  - Affects participant's daily activity and may require ongoing treatment/therapy
  - Hospitalization possible

- **Characteristics of Life threatening**:
  - Extreme limitation in activity
  - Significant assistance required
  - Serious medical intervention and/or therapy required
  - Hospitalization or hospice care probable

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Determining Causality

POSSIBLY RELATED	DEFINITELY RELATED
Defined as meeting <u>any</u> of the following conditions:	Defined as meeting **<u>all four</u>** of the following conditions:
Has a reasonable temporal relationship to intervention	Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure
Could not readily have been produced by the research participant's clinical state or have been due to environmental or other interventions;	Could not readily have been produced by the research participant's clinical state or have been due to environmental or other interventions;
Follows a known pattern of response to intervention.	Follows a known pattern of response to intervention;

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Unanticipated Problems (UPs)

- Unanticipated/Unexpected Problem (UP):
  - Any incident, experience, or outcome that meets <u>all</u> of the following criteria:
    - In terms of nature, severity, or frequency given:
      - the research procedures that are described in the protocol-related documents, i.e. IRB-approved research protocol, informed consent form; and
      - the characteristics of the subject population being studied
      - Some UPs involve social or economic harm instead of the physical or psychological harm associated with adverse events
- Some UPs place subjects or others at increased *risk* of harm, but no harm occurs
- A UP will likely warrant consideration of substantive changes in the research protocol and/or informed consent process/document or other corrective actions in order to protect the safety, welfare and rights of subjects or others

Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS)

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Responding to an Unanticipated Problem

- **Changes to the protocol initiated by the investigator prior to obtaining sponsor approval to eliminate apparent immediate hazards to subjects**
- **Modification of inclusion or exclusion criteria to mitigate the newly identified risks**
- **Implementation of additional procedures for monitoring subjects**
- **Suspension of enrollment of new subjects**
- **Suspension of research procedures in currently enrolled subjects**
- **Modification of Informed Consent Form (ICF) to include a description of newly recognized risks**
- **Re-consenting**

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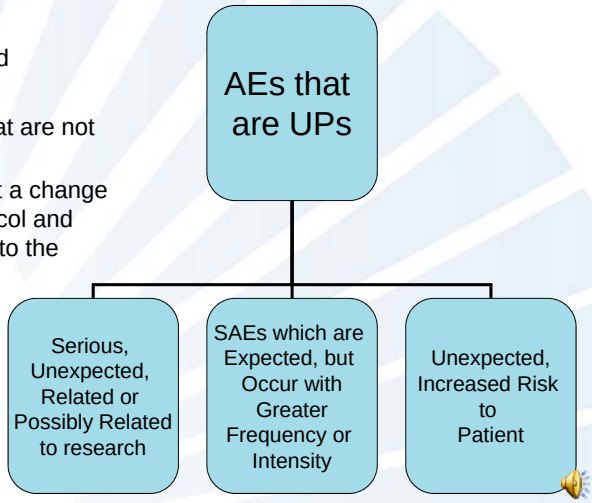
How do UPs relate to AEs?

- Most AEs are expected
- Few AEs are UPs
- UPs include events that are not AEs
- Some UPs will warrant a change in IRB-approved protocol and informed consent due to the change in risk



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Investigator Responsibilities

- Report must include a detailed accountability of the event, including some basic elements:
  - Elicit AE/ SAE During Patient Visit

    Ex. “Do you feel different in any way since starting the new treatment/the last visit?”.
  - Report Serious Adverse Event (SAE) immediately to sponsor *(ICH E6 4.11)*
  - Notify IRB or Ethics Committee at the study site of such SAE
- AEs should be recorded in the CRF and the source documents
- Report any Investigator Notifications to IRB
- Ensure adequate follow-up and inform sponsor

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Sponsor’s responsibilities

- Adequate training of investigator and team
- Expedited reporting of all SAEs to FDA
- Verification of the SAE form data against source documents
- Consistency of SAE form data with the CRF data
- Generate “Investigator Notifications” when required
- Generate periodic safety updates

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Writing the report

- Wherever possible, adverse events should be described in terms of a change in the status or diagnosis NOT the symptoms.
- It is an ongoing event not a static occurrence
  - Example: “anaphylaxis” rather than “swelling of throat”
  - Example: “RSV” rather than “fever, coughing, wheezing”

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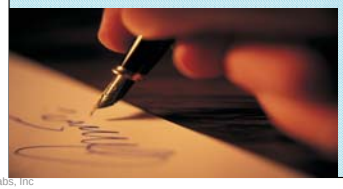
Documentation of SAE

- **ALL documents must match and be complete:**
  - SAE form
  - Adverse Event Case Report Form
  - Source documents

- **Principal Investigator must sign SAE report**



Slide 19

MSOffice2 Change examples
, 12/31/2007

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Assessing Intensity of the Adverse Event

- AE needs to be assessed by the investigator using the pre-defined classification system from the protocol
- If a grading system is not identified, follow this suggestion:
  - Mild – no medical interventions required, short-lasting discomfort and does not interfere with the patient's daily activities
  - Moderate – activity may be limited and subject may need minimal medical therapy, intervention or assistance
  - Severe – definitely limits subject's daily activity with may require hospitalization and/or intervention/therapy
  - Life-threatening – will require assistance, serious medical attention, and hospitalization

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Expedited Reports for Serious Adverse Events

- According to the IRB, WHO IDMC, and CIOMS-I, and FDA, the minimum should be included in the SAE expedited report:
  - "Identifiable patient"
  - Name of investigational product that probably caused the SAE
  - Identifiable reporting source
  - Event or outcome that can be identified as serious and unexpected and for which, inclinical investigation cases there is a reasonable suspected causal relationship,"

    Clinical Safety Data Management:
    Definitions and Standards for Expedited Reporting.
    Guidance E2A. Attachment 1. ICH
  - Any additional information, as suggested by Attachment 1, should also be included in the report, if it is available

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What else should be included in the report?

- All AEs must be reported on AE case report forms, which should include:
  - AE term (ex. unexpected, expected serious)
  - Onset date, offset date
  - Severity
  - Probability of relationship to test article
  - Test article administration
  - Status/outcome and date
  - Treatment given
  - Follow-up care plan

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Reporting Time Frame for SAEs

- Report any SAEs to Sponsor and IRB within 24 hours or as soon as possible
- FDA Investigational Drug Reporting:
  - The Sponsor-PI must provide the following reports in a timely manner to the FDA, IRB's and or other Investigators.
  - Drug Studies:
    - Sponsor-PI must inform the FDA of any SAE that is unexpected and related
  - Telephone report within 3 days of occurrence
  - Written report within 10 days. Identify all previous IND safety reports concerning similar SAE's and their relevance to this event

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Reporting for drugs covered by an Investigational New Drug Application (IND):

--Investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately [21CFR312.64(b)].

--Investigator shall assure that he or she will promptly report to the IRB all unanticipated risks to human subjects or others (21CFR312.66).

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Consequences of reporting out of timeframe or incomplete reporting

- PI and research staff will receive an email from sponsor reminding them of the reporting time-frame requirements
- Investigator receives a letter from the IRB
- Review by the full IRB committee who will decide on the course of action

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Consequences of reporting out of timeframe or incomplete reporting

- Course of action may include (but is not limited to) the following:
  - Requesting written response from the PI
  - Requesting presence of PI at next IRB meeting to address the issue with the committee
  - Scheduling an audit of the PI's research
  - Suspension of enrollment into one or more of the PI's ongoing studies
  - Report of non-compliance to IEC and/or the FDA

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Summary

- Adverse Events should be reported with regard to their severity
- Adverse Events should be classified by type (unexpected or expected)
- Reporting to the investigator is necessary
- Report to the proper regulatory authorities and sponsor
- Follow up care for subjects is essential, sometimes for life

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References

- Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS)
- Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection. DHHS.
- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. E2A. International Conference on Harmonisation
- Guidance for Industry: Good Clinical Practices. E6. ICH.
- Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting. E2D. ICH.

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CLINICAL DRUG DEVELOPMENT

References

- Investigational New Drug Application. Title 21 CFR Part 312. U.S. FDA.
- Investigational Device Exemptions. Title 21 CFR Part 812. U.S. FDA.
- Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials. National Institutes of Health.

U.S. Food and Drug Administration

Regulatory Information

A Guide to Informed Consent - Information Sheet

Guidance for Institutional Review Boards and Clinical Investigators

Contents

Consent Document Content

For studies that are subject to the requirements of the FDA regulations, the informed consent documents should meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25(a), and each of the six elements of 21 CFR 50.25(b) that is appropriate to the study. IRBs have the final authority for ensuring the adequacy of the information in the informed consent document.

IRB standard format

Many IRBs have developed standard language and/or a standard format to be used in portions of all consent documents. Standard language is typically developed for those elements that deal with confidentiality, compensation, answers to questions, and the voluntary nature of participation. Each investigator should determine the local IRB's requirements before submitting a study for initial review. Where changes are needed from the standard paragraphs or format, the investigator can save time by anticipating the local IRB's concerns and explaining in the submission to the IRB why the changes are necessary.

Sponsor-prepared sample consent documents

Sample or draft consent documents may be developed by a sponsor or cooperative study group. However, the IRB of record is the final authority on the content of the consent documents that is presented to the prospective study subjects.

Investigational New Drug Applications (IND) submitted to FDA are not required to contain a copy of the consent document. If the sponsor submits a copy, or if FDA requests a copy, the Agency will review the document and may comment on the document's adequacy.

For significant risk medical devices, the consent document is considered to be a part of the investigational plan in the Application for an Investigational Device Exemption (IDE). FDA always reviews these consent documents. The Agency's review is generally limited to ensuring the presence of the required elements of informed consent and the absence of exculpatory language. Any substantive changes to the document made by an IRB must be submitted to FDA (by the sponsor) for review and approval.

Revision of Consent Documents during the study

Study protocols are often changed during the course of the study. When these changes require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. While not required by FDA regulations, some IRBs stamp the final copy of the consent document with the approval date. The investigator then photocopies the consent document for use. [Note: the wording of the regulations is provided in *italics*, followed by explanatory comments.]

21 CFR 50.20 General requirements for informed consent

Except as provided in ß50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

The IRB should ensure that technical and scientific terms are adequately explained or that common terms are substituted. The IRB should ensure tha the informed consent document properly translates complex scientific concepts into simple concepts that the typical subject can read and comprehend.

Although not prohibited by the FDA regulations, use of the wording, "I understand..." in informed consent documents may be inappropriate as many prospective subjects will not "understand" the scientific and medical significance of all the statements. Consent documents are more understandable they are written just as the clinical investigator would give an oral explanation to the subject, that is, the subject is addressed as "you" and the clinical investigator as "I/we." This second person writing style also helps to communicate that there is a choice to be made by the prospective subject. Use of first person may be interpreted as presumption of subject consent, i.e., the subject has no choice. Also, the tone of the first person "I understand" style seems to misplace emphasis on legal statements rather than on explanatory wording enhancing the subject's comprehension.

Subjects are not in a position to judge whether the information provided is complete. Subjects may certify that they understand the statements in th consent document and are satisfied with the explanation provided by the consent process (e.g., "I understand the statements in this informed consent document)." They should not be required to certify completeness of disclosure (e.g., "This study has been fully explained to me," or, "I fully understand the study.")

Consent documents should not contain unproven claims of effectiveness or certainty of benefit, either explicit or implicit, that may unduly influence potential subjects. Overly optimistic representations are misleading and violate FDA regulations concerning the promotion of investigational drugs [21 CFR 312.7] or investigational devices [21 CFR 812.7(d)] as well as the requirement to minimize the possibility of coercion or undue influence [21 CFR 50.20].

FDA approval of studies

Investigational drug and biologic studies are not officially approved by FDA. When a sponsor submits a study to FDA as part of the initial application for an investigational new drug (IND), FDA has thirty days to review the application and place the study on "hold" if there are any obvious reasons why the proposed study should not be conducted. Therefore, subjects are likely to impute a greater involvement by the Agency in a research study than actually exists if phrases such as, "FDA has given permission..." or "FDA has approved..." are used in consent documents. If FDA does not place the study on hold within the thirty day period, the study may begin (with IRB approval).

FDA also believes that an explicit statement that an IRB has approved solicitation of subjects to participate in research could mislead or unduly induc subjects. Subjects might think that, because the IRB had approved the research, there is no need to evaluate the study for themselves to determine whether or not they should participate.

Non-English Speaking Subjects

To meet the requirements of 21 CFR 50.20, the informed consent document should be in language understandable to the subject (or authorized representative). When the consent interview is conducted in English, the consent document should be in English. When the study subject population includes non-English speaking people or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB should require a translated consent document to be prepared and assure that the translation is accurate. As required by 21 CFR 50.27, a copy of the consent document must be given to each subject. In the case of non-English speaking subjects, this would be the translated document. While a translator may be helpful in facilitating conversation with a non-English speaking subject, routine ad hoc translation of the consent document should not be substituted for a written translation.

If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation. Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective. I investigators enroll subjects without an IRB approved written translation, a "short form" written consent document, in a language the subject understands, should be used to document that the elements of informed consent required by 21 CFR 50.25 were presented orally. The required signatures on a short form are stated in 21 CFR 50.27(b)(2).

Illiterate English-Speaking Subjects

A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document, when consistent with applicable state law.

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

Assent of children

Although not addressed in the regulations, FDA believes that IRBs should consider whether to require the approval of older children before they are enrolled in a research study. For research with children, some IRBs have required that two consent documents be developed. One for obtaining the parents permission and one, which outlines the study in simplified language, for obtaining the assent of children who can understand the concepts involved. Although not required by FDA regulations, the HHS regulations for conduct of studies in children may be used as guidance [45 CFR 46, Subpart D].

21 CFR 50.25 Elements of informed consent

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

The statement that the study involves research is important because the relationship between patient-physician is different than that between subjec -investigator. Any procedures relating solely to research (e.g., randomization, placebo control, additional tests) should be explained to the subjects. The procedures subjects will encounter should be outlined in the consent document, or an explanation of the procedures, such as a treatment chart, may be attached to and referenced in the consent document.

Consent documents for studies of investigational articles should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies, are not appropriate whe the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, consent documents shoul include that purpose, but should not contain claims of effectiveness.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

The risks of procedures relating solely to research should be explained in the consent document. The risks of the tests required in the study protocol should be explained, especially for tests that carry significant risk of morbidity/mortality themselves. The explanation of risks should be reasonable and should not minimize reported adverse effects.

The explanation of risks of the test article should be based upon information presented in documents such as the protocol and/or investigator's brochure, package labeling, and previous research study reports. For IND studies, the IRB should assure that the clinical investigator submits the investigator's brochure (when one exists) with the other study materials for review.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

The description of benefits to the subject should be clear and not overstated. If no direct benefit is anticipated, that should be stated. The IRB should be aware that this element includes a description not only of the benefits to the subject, but to "others" as well. This may be an issue when benefits accruing to the investigator, the sponsor, or others are different than that normally expected to result from conducting research. Thus, if these benefits may be materially relevant to the subject's decision to participate, they should be disclosed in the informed consent document.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

To enable a rational choice about participating in the research study, subjects should be aware of the full range of options available to them. Consent documents should briefly explain any pertinent alternatives to entering the study including, when appropriate, the alternative of supportive care with no additional disease-directed therapy. While this should be more than just a list of alternatives, a full risk/benefit explanation of alternatives may no be appropriate to include in the written document. The person(s) obtaining the subjects' consent, however, should be able to discuss available

alternatives and answer questions that the subject may raise about them. As with other required elements, the consent document should contain sufficient information to ensure an informed decision.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

Study subjects should be informed of the extent to which the institution intends to maintain confidentiality of records identifying the subjects. In addition, they should be informed that FDA may inspect study records (which include individual medical records). If any other entity, such as the sponsor of the study, may gain access to the study records, the subjects should be so informed. The consent document may, at the option of the IRE state that subjects' names are not routinely required to be divulged to FDA. When FDA requires subject names, FDA will treat such information as confidential, but on rare occasions, disclosure to third parties may be required. Therefore, absolute protection of confidentiality by FDA should not be promised or implied. Also, consent documents should not state or imply that FDA needs clearance or permission from the subject for access. When clinical investigators conduct a study for submission to FDA, they agree to allow FDA access to the study records. Informed consent documents should make it clear that, by participating in research, the subject's records automatically become part of the research database. Subjects do not have the option to keep their records from being audited/reviewed by FDA.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

Informed consent documents should describe any compensation or medical treatments that will be provided if injury occurs. If specific statements cannot be made (e.g., each case is likely to require a different response), the subjects should be informed where further information may be obtained. The consent should also indicate whether subjects will be billed for the cost of such medical treatments. When costs will be billed, statements such as "will be billed to you or your insurer in the ordinary manner," "the sponsor has set some funds aside for medical costs related to.... Here's how to apply for reimbursement if you think you might be eligible" or "no funds have been set aside..." are preferred. Statements such as: "will be the responsibility of you or your insurance company" or "compensation is not available," could appear to relieve the sponsor or investigator of liability for negligence, see 21 CFR 50.20.

Compensation v. Waiver of Subject's Rights

The consent document must explain whether there is compensation available in case of injury but must not waive or appear to waive the rights of the subject or release or appear to release those conducting the study from liability for negligence. When no system has been set up to provide funds, the preferred wording is: "no funds have been set aside for" "[the cost] will be billed to you or your insurance," or similar wording that explains the provisions or the process. Wording such as: "will be your responsibility or that of your third-party payor" has been erroneously interpreted by some subjects to mean the insurance company is required to pay.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

This requirement contains three components, each of which should be specifically addressed. The consent document should provide the name of a specific office or person and the telephone number to contact for answers to questions about: 1) the research subjects' rights; 2) a research-related injury; and 3) the research study itself. It is as important for the subject to know why an individual should be contacted as it is for the subject to know whom to contact. Although a single contact might be able to fulfill this requirement, IRBs should consider requiring that the person(s) named for questions about research subjects' rights not be part of the research team as this may tend to inhibit subjects from reporting concerns and discovering possible problems.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

This element requires that subjects be informed that they may decline to participate or to discontinue participation at any time without penalty or los of benefits. Language limiting the subject's right to withdraw from the study should not be permitted in consent documents. If the subjects who withdraw will be asked to permit follow-up of their condition by the researchers, the process and option should be outlined in the consent document.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

A statement that there may be unforeseen risks to the embryo or fetus may not be sufficient if animal data are not available to help predict the risk to a human fetus. Informed consent documents should explain that mutagenicity (the capability to induce genetic mutations) and teratogenicity (the capability to induce fetal malformations) studies have not yet been conducted/completed in animals. [Note: The lack of animal data does not constitute a valid reason for restricting entry of women of childbearing potential into a clinical trial.] Subjects, both women and men, need to understand the danger of taking a drug whose effects on the fetus are unknown. If relevant animal data are available, however, the significance should be explained to potential subjects. Investigators should ensure that the potential risks that the study poses are adequately explained to subjects who are asked to enter a study. If measures to prevent pregnancy should be taken while in the study, that should be explained.

FDA guidance on the inclusion of women in clinical trials [58 FR 39406] now gives IRBs broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA urges IRBs to question any study that appears to limit enrollment based on gender and/or minority status. Statements such as, "you may not participate in this research study if you are a woman who could become pregnant" should not routinely be included in informed consent documents.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

When applicable, subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject's consent. An unexplained statement that the investigator and/or sponsor may withdraw subjects at any time, does not adequately inform the subjects of anticipated circumstances for such withdrawal.

A statement that the investigator may withdraw subjects if they do not "follow study procedures" is not appropriate. Subjects are not in a position to know all the study procedures. Subjects may be informed, however, that they may be withdrawn if they do not follow the instructions given to them by the investigator.

(3) Any additional costs to the subject that may result from participation in the research.

If the subjects may incur an additional expense because they are participating in the research, the costs should be explained. IRBs should consider that some insurance and/or other reimbursement mechanisms may not fund care that is delivered in a research context.

(4) The consequences of a subjects' decision to withdraw from the research and procedures for orderly termination of participation by the subject.

When withdrawal from a research study may have deleterious effects on the subject's health or welfare, the informed consent should explain any withdrawal procedures that are necessary for the subject's safety and specifically state why they are important to the subject's welfare. An unexplained statement that the subject will be asked to submit to tests prior to withdrawal, does not adequately inform the subjects why the tests are necessary for the subject's welfare.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

When it is anticipated that significant new findings that would be pertinent to the subject's continued participation are likely to occur during the subject's participation in the study, the IRB should determine that a system, or a reasonable plan, exists to make such notification to subjects.

(6) The approximate number of subjects involved in the study.

If the IRB determines that the numbers of subjects in a study is material to the subjects' decision to participate, the informed consent document should state the approximate number of subjects involved in the study.

The Consent Process

Informed consent is more than just a signature on a form, it is a process of information exchange that may include, in addition to reading and signing the informed consent document, subject recruitment materials, verbal instructions, question/answer sessions and measures of subject understanding. Institutional Review Boards (IRBs), clinical investigators, and research sponsors all share responsibility for ensuring that the informed consent process is adequate. Thus, rather than an endpoint, the consent document should be the basis for a meaningful exchange between the investigator and the subject.

The clinical investigator is responsible for ensuring that informed consent is obtained from each research subject before that subject participates in the research study. FDA does not require the investigator to personally conduct the consent interview. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another individual knowledgeable about the research.

In addition to signing the consent, the subject/representative should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the subject began participation in the study. If consent is obtained the same day that the subject's involvement in the study begins, the subject's medical records/case report form should document that consent was obtained prior to participation in the research. A copy of the consent document must be provided to the subject and the original signed consent document should be retained in the study records. Note that the FDA regulations do not require the subject's copy to be a signed copy, although a photocopy with signature(s) is preferred.

The IRB should be aware of who will conduct the consent interview. The IRB should also be informed of such matters as the timing of obtaining informed consent and of any waiting period (between informing the subject and obtaining the consent) that will be observed.

The consent process begins when a potential research subject is initially contacted. Although an investigator may not recruit subjects to participate in a research study before the IRB reviews and approves the study, an investigator may query potential subjects to determine if an adequate number of potentially eligible subjects is available.

21 CFR 50.27 Documentation of Informed Consent

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but , in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A short form written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

The informed consent documentation requirements [21 CFR 50.27] permit the use of either a written consent document that embodies the elements of informed consent or a "short form" stating that the elements of informed consent have been presented orally to the subject. Whichever document is used, a copy must be given to the person signing the document.

When a short form consent document is to be used [21 CFR 50.27(b)(2)], the IRB should review and approve the written summary of the full information to be presented orally to the subjects. A witness is required to attest to the adequacy of the consent process and to the subject's voluntary consent. Therefore, the witness must be present during the entire consent interview, not just for signing the documents. The subject or the subject's legally authorized representative must sign and date the short form. The witness must sign both the short form and a copy of the summary and the person actually obtaining the consent must sign a copy of the summary. The subject or the representative must be given a copy of the summary as well as a copy of the short form. While the regulations do not prohibit the use of multiple consent documents, FDA suggests that they be used with caution. Multiple consent documents may be confusing to a research subject and if, inadvertently, one document is not presented, critical information may not be relayed to the research subject. For some studies, however, the use of multiple documents may improve subject understanding by "staging" information in the consent process. This process may be useful for studies with separate and distinct, but linked, phases through which the subject may proceed. If this technique is used, the initial document should explain that subjects will be asked to participate in the additional phases. It should be clear whether the phases are steps in one study or separate but interrelated studies. For certain types of studies, the Agency encourages the process of renewing the consent of subjects.

Also see these FDA information sheets:

"Sponsor-Investigator-IRB Interrelationship" [1]

"Acceptance of Foreign Clinical Studies" [2]

"Emergency Use of an Investigational Drug or Biologic" [3]

"Screening Tests Prior to Study Enrollment" [4]

"Recruiting Study Subjects" [5]

"Payment to Research Subjects" [6]

"Evaluation of Gender Differences in Clinical Investigations" [7]

"Comparison of FDA and HHS Human Subject Protection Regulations [8]"

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WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

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Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee.

Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician

relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Protection of Human Subjects

Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four day period of discussions that were held in February 1976 at the Smithsonian Institute's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of ethical problems that surround the conduct

of research with human subjects. By publishing the Report in the **Federal Register**, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of the Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Goverment Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

- Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
- Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
- Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
- Dorothy L. Height, President, National Council of Negro Women, Inc.
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- Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
- Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
- * David W. Louisell, J.D., Professor of Law, University of California at Berkeley.
- Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
- Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.
- * Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

* Deceased.

Belmont Report

Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes (1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals (2). By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions

to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project(3).

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. ***Respect for Persons***. Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

   An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

   However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals

lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. ***Beneficence***. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

   The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes is possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. ***Justice***.-- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of"fairness in distribution" or"what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

   Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions

have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. ***Informed Consent.*** -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

   While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

   Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement

offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the

subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled .

2. ***Assessment of Risks and benefits***.--- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and

comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike"risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.

This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished wit.h as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject or, in some rare cases. to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. ***Selection of Subjects***. --- Just as the principle of respect for persons finds expression in the requirements for consent. and the principle of beneficence in risk, benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

   Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized

mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

footnote1
Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

footnote2
Although practice usually involves interventions designed solely to enhance the well being of a

particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

footnote3

Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

[Code of Federal Regulations]

[Title 21, Volume 1]

[Revised as of April 1, 2010]

[CITE: 21CFR11]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A--General Provisions

Sec. 11.1 Scope.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with 11.2, unless paper records are specifically required.

(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

(f) This part does not apply to records required to be established or maintained by 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

[62 FR 13464, Mar. 20, 1997, as amended at 69 FR 71655, Dec. 9, 2004]

Sec. 11.2 Implementation

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:

(1) The requirements of this part are met; and

(2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Sec. 11.3 Definitions.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms also apply to this part:

(1)*Act* means the Federal Food, Drug, and Cosmetic Act (secs. 201-903 (21 U.S.C. 321-393)).

(2)*Agency* means the Food and Drug Administration.

(3)*Biometrics* means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

(4)*Closed system* means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

(5)*Digital signature* means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

(6)*Electronic record* means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

(7)*Electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

(8)*Handwritten signature* means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

(9)*Open system* means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B--Electronic Records

Sec. 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Sec. 11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Sec. 11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and

(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout)

Sec. 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C--Electronic Signatures

Sec. 11.100 General requirements.

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

(1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.

(2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Sec. 11.200 Electronic signature components and controls.

(a) Electronic signatures that are not based upon biometrics shall:

(1) Employ at least two distinct identification components such as an identification code and password.

(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.

(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.

(2) Be used only by their genuine owners; and

(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Sec. 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.
Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

[Code of Federal Regulations]

[Title 21, Volume 1]

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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL

PART 50 PROTECTION OF HUMAN SUBJECTS

Subpart A--General Provisions

Sec. 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999; 66 FR 20597, Apr. 24, 2001]

Sec. 50.3 Definitions.

As used in this part:

(a)*Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040*et seq.* as amended (21 U.S.C. 321-392)).

(b)*Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An*Application for an Investigational Device Exemption,* described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.

(23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, or for a health claim, described in 101.70 of this chapter.

(25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.

(c)*Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d)*Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e)*Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f)*Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g)*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h)*Institution* means any public or private entity or agency (including Federal, State, and other agencies). The word*facility* as used in section 520(g) of the act is deemed to be synonymous with the term*institution* for purposes of this part.

(i)*Institutional review board* (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase*institutional review committee* as used in section 520(g) of the act.

(j)*Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(k)*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(l)*Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's particpation in the procedure(s) involved in the research.

(m)*Family member* means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

(n)*Assent* means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

(o)*Children* means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

(p)*Parent* means a child's biological or adoptive parent.

(q)*Ward* means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

(r)*Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in 50.25.

(s)*Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51528, Oct. 2, 1996; 62 FR 39440, July 23, 1997; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 66 FR 20597, Apr. 24, 2001]

Subpart B--Informed Consent of Human Subjects

Sec. 50.20 General requirements for informed consent

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

[46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

Sec. 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in theFederal Registerdescribing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

(e)(1) Obtaining informed consent for investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents will be deemed feasible unless, before use of the test article, both the investigator (e.g., clinical laboratory director or other responsible individual) and a physician who is not otherwise participating in the clinical investigation make the determinations and later certify in writing all of the following:

(i) The human subject is confronted by a life-threatening situation necessitating the use of the investigational in vitro diagnostic device to identify a chemical, biological, radiological, or nuclear agent that would suggest a terrorism event or other public health emergency.

(ii) Informed consent cannot be obtained from the subject because:

(A) There was no reasonable way for the person directing that the specimen be collected to know, at the time the specimen was collected, that there would be a need to use the investigational in vitro diagnostic device on that subject's specimen; and

(B) Time is not sufficient to obtain consent from the subject without risking the life of the subject.

(iii) Time is not sufficient to obtain consent from the subject's legally authorized representative.

(iv) There is no cleared or approved available alternative method of diagnosis, to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.

(2) If use of the investigational device is, in the opinion of the investigator (e.g., clinical laboratory director or other responsible person), required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (e)(1) of this section in advance of using the investigational device, the determinations of the investigator shall be made and, within 5 working days after the use of the device, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(3) The investigator must submit the documentation required in paragraph (e)(1) or (e)(2) of this section to the IRB within 5 working days after the use of the device.

(4) An investigator must disclose the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in the report to the subject's health care provider and in any report to public health authorities. The investigator must provide the IRB with the information required in 50.25 (except for the information described in 50.25(a)(8)) and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and public health authorities.

(5) The IRB is responsible for ensuring the adequacy of the information required in section 50.25 (except for the information described in 50.25(a)(8)) and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.

(6) No State or political subdivision of a State may establish or continue in effect any law, rule, regulation or other requirement that informed consent be obtained before an investigational in vitro diagnostic device may be used to identify chemical, biological, radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that is different from, or in addition to, the requirements of this regulation.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999; 71 FR 32833, June 7, 2006]

Sec. 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally

authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

Sec. 50.25 Elements of informed consent.

(a)*Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b)*Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

Sec. 50.27 Documentation of informed consent.

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A*short form* written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

[46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]

Subpart C [Reserved]

Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of this subpart D.

Sec. 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in 50.1 and56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:

(a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.

(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(1) The clinical investigation involves no more than minimal risk to the subjects;

(2) The waiver will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under 50.51 or 50.52.

(2) Where clinical investigations are covered by 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

Sec. 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under 50.53 or 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.
Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

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[CITE: 21CFR54]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 54 FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS

Sec. 54.1 Purpose.

(a) The Food and Drug Administration (FDA) evaluates clinical studies submitted in marketing applications, required by law, for new human drugs and biological products and marketing applications and reclassification petitions for medical devices.

(b) The agency reviews data generated in these clinical studies to determine whether the applications are approvable under the statutory requirements. FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study. This section and conforming regulations require an applicant whose submission relies in part on clinical data to disclose certain financial arrangements between sponsor(s) of the covered studies and the clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered studies. FDA will use this information, in conjunction with information about the design and purpose of the study, as well as information obtained through on-site inspections, in the agency's assessment of the reliability of the data.

Sec. 54.2 Definitions.

For the purposes of this part:

(a)*Compensation affected by the outcome of clinical studies* means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.

(b)*Significant equity interest in the sponsor of a covered study* means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

(c)*Proprietary interest in the tested product* means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

(d)*Clinical investigator* means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

(e)*Covered clinical study* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

(f)*Significant payments of other sorts* means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study.

(g)*Applicant* means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

(h)*Sponsor of the covered clinical study* means the party supporting a particular study at the time it was carried out.

[63 FR 5250, Feb. 2, 1998, as amended at 63 FR 72181, Dec. 31, 1998]

Sec. 54.3 Scope.

The requirements in this part apply to any applicant who submits a marketing application for a human drug, biological product, or device and who submits covered clinical studies. The applicant is responsible for making the appropriate certification or disclosure statement where the applicant either contracted with one or more clinical investigators to conduct the studies or submitted studies conducted by others not under contract to the applicant.

Sec. 54.4 Certification and disclosure requirements.

For purposes of this part, an applicant must submit a list of all clinical investigators who conducted covered clinical studies to determine whether the applicant's product meets FDA's marketing requirements, identifying those clinical investigators who are full-time or part-time employees of the sponsor of each covered study. The applicant must also completely and accurately disclose or certify information concerning the financial interests of a clinical investigator who is not a full-time or part-time employee of the sponsor for each covered clinical study. Clinical investigators subject to investigational new drug or investigational device exemption regulations must provide the sponsor of the study with sufficient accurate information needed to allow subsequent disclosure or certification. The applicant is required to submit for each clinical investigator who participates in a covered study, either a certification that none of the financial arrangements described in 54.2 exist, or disclose the nature of those arrangements to the agency. Where the applicant acts with due diligence to obtain the information required in this section but is unable to do so, the applicant shall certify that despite the applicant's due diligence in attempting to obtain the information, the applicant was unable to obtain the information and shall include the reason.

(a) The applicant (of an application submitted under sections 505, 506, 510(k), 513, or 515 of the Federal Food, Drug, and Cosmetic Act, or section 351 of the Public Health Service Act) that relies in whole or in part on clinical studies shall submit, for each clinical investigator who participated in a covered clinical study, either a certification described in paragraph (a)(1) of this section or a disclosure statement described in paragraph (a)(3) of this section.

(1) Certification: The applicant covered by this section shall submit for all clinical investigators (as defined in 54.2(d)), to whom the certification applies, a completed Form FDA 3454 attesting to the absence of financial interests and arrangements described in paragraph (a)(3) of this section. The form shall be dated and signed by the chief financial officer or other responsible corporate official or representative.

(2) If the certification covers less than all covered clinical data in the application, the applicant shall include in the certification a list of the studies covered by this certification.

(3) Disclosure Statement: For any clinical investigator defined in 54.2(d) for whom the applicant does not submit the certification described in paragraph (a)(1) of this section, the applicant shall submit a completed Form FDA 3455 disclosing completely and accurately the following:

(i) Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

(ii) Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

(iii) Any proprietary interest in the tested product held by any clinical investigator involved in a study;

(iv) Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and

(v) Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

(b) The clinical investigator shall provide to the sponsor of the covered study sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements as required in paragraph (a) of this section. The investigator shall promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

(c) Refusal to file application. FDA may refuse to file any marketing application described in paragraph (a) of this section that does not contain the information required by this section or a certification by the applicant that the applicant has acted with due diligence to obtain the information but was unable to do so and stating the reason.

[63 FR 5250, Feb. 2, 1998; 63 FR 35134, June 29, 1998, as amended at 64 FR 399, Jan. 5, 1999]

Sec. 54.5 Agency evaluation of financial interests.

(a)*Evaluation of disclosure statement.* FDA will evaluate the information disclosed under 54.4(a)(2) about each covered clinical study in an application to determine the impact of any disclosed financial interests on the reliability of the study. FDA may consider both the size and nature of a disclosed financial interest (including the potential increase in the value of the interest if the product is approved) and steps that have been taken to minimize the potential for bias.

(b)*Effect of study design.* In assessing the potential of an investigator's financial interests to bias a study, FDA will take into account the design and purpose of the study. Study designs that utilize such approaches as multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurement of endpoints by someone other than the investigator may adequately protect against any bias created by a disclosable financial interest.

(c)*Agency actions to ensure reliability of data.* If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data including:

(1) Initiating agency audits of the data derived from the clinical investigator in question;

(2) Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on overall study outcome;

(3) Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

(4) Refusing to treat the covered clinical study as providing data that can be the basis for an agency action.

Sec. 54.6 Recordkeeping and record retention

(a)*Financial records of clinical investigators to be retained.* An applicant who has submitted a marketing application containing covered clinical studies shall keep on file certain information pertaining to the financial interests of clinical investigators who conducted studies on which the application relies and who are not full or part-time employees of the applicant, as follows:

(1) Complete records showing any financial interest or arrangement as described in 54.4(a)(3)(i) paid to such clinical investigators by the sponsor of the covered study.

(2) Complete records showing significant payments of other sorts, as described in 54.4(a)(3)(ii), made by the sponsor of the covered clinical study to the clinical investigator.

(3) Complete records showing any financial interests held by clinical investigators as set forth in 54.4(a)(3)(iii) and (a)(3)(iv).

(b)*Requirements for maintenance of clinical investigators' financial records.* (1) For any application submitted for a covered product, an applicant shall retain records as described in paragraph (a) of this section for 2 years after the date of approval of the application.

(2) The person maintaining these records shall, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to and copy and verify these records.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c-360j, 371, 372, 373, 374, 375, 376, 379; 42 U.S.C. 262.
Source: 63 FR 5250, Feb. 2, 1998, unless otherwise noted.

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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL

PART 56 INSTITUTIONAL REVIEW BOARDS

Subpart A--General Provisions

Sec. 56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[46 FR 8975, Jan. 27, 1981, as amended at 64 FR 399, Jan. 5, 1999; 66 FR 20599, Apr. 24, 2001]

Sec. 56.102 Definitions.

As used in this part:

(a)*Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040*et seq.,* as amended (21 U.S.C. 321-392)).

(b)*Application for research or marketing permit* includes:

(1) A color additive petition, described in part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.35.

(3) A food additive petition, described in part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) An application for a biologics license, described in part 601 of this chapter.

(11) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601 of this chapter.

(12) An Application for an Investigational Device Exemption, described in part 812.

(13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861.

(15) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(16) A product development protocol for a medical device for human use, described in section 515 of the act.

(17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.

(19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.

(20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003.

(21) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(22) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, and for a health claim, described in 101.70 of this chapter.

(23) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.

(c)*Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms*research, clinical research, clinical study, study,* and*clinical investigation* are deemed to be synonymous for purposes of this part.

(d)*Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e)*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f)*Institution* means any public or private entity or agency (including Federal, State, and other agencies). The term*facility* as used in section 520(g) of the act is deemed to be synonymous with the term*institution* for purposes of this part.

(g)*Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase*institutional review committee* as used in section 520(g) of the act.

(h)*Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i)*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j)*Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k)*Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l)*Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

(m)*IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 65 FR 52302, Aug. 29, 2000; 66 FR 20599, Apr. 24, 2001; 74 FR 2368, Jan. 15, 2009]

Sec. 56.103 Circumstances in which IRB review is required.

(a) Except as provided in 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

Sec. 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

Sec. 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B--Organization and Personnel

Sec. 56.106 Registration.

(a)*Who must register* ? Each IRB in the United States that reviews clinical investigations regulated by FDA under sections 505(i) or 520(g) of the act and each IRB in the United States that reviews clinical investigations that are intended to support applications for research or marketing permits for FDA-regulated products must register at a site maintained by the Department of Health and Human Services (HHS). (A research permit under section 505(i) of the act is usually known as an investigational new drug application (IND), while a research permit under section 520(g) of the act is usually known as an investigational device exemption (IDE).) An individual authorized to act on the IRB's behalf must submit the registration information. All other IRBs may register voluntarily.

(b)*What information must an IRB register* ? Each IRB must provide the following information:

(1) The name, mailing address, and street address (if different from the mailing address) of the institution operating the IRB and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer of that institution who is responsible for overseeing activities performed by the IRB;

(2) The IRB's name, mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address; each IRB chairperson's name, phone number, and electronic mail address; and the name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.

(3) The approximate number of active protocols involving FDA-regulated products reviewed. For purposes of this rule, an "active protocol" is any protocol for which an IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure during the preceding 12 months; and

(4) A description of the types of FDA-regulated products (such as biological products, color additives, food additives, human drugs, or medical devices) involved in the protocols that the IRB reviews.

(c)*When must an IRB register* ? Each IRB must submit an initial registration. The initial registration must occur before the IRB begins to review a clinical investigation described in paragraph (a) of this section. Each IRB must renew its registration every 3 years. IRB registration becomes effective after review and acceptance by HHS.

(d)*Where can an IRB register* ? Each IRB may register electronically through*http://ohrp.cit.nih.gov/efile* . If an IRB lacks the ability to register electronically, it must send its registration information, in writing, to the Good Clinical Practice Program (HF-34), Office of Science and Health Coordination, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(e)*How does an IRB revise its registration information* ? If an IRB's contact or chair person information changes, the IRB must revise its registration information by submitting any changes in that information within 90 days of the change. An IRB's decision to review new types of FDA-regulated products (such as a decision to review studies pertaining to food additives whereas the IRB previously reviewed studies pertaining to drug products), or to discontinue reviewing clinical investigations regulated by FDA is a change that must be reported within 30 days of the change. An IRB's decision to disband is a change that must be reported within 30 days of permanent cessation of the IRB's review of research. All other information changes may be reported when the IRB renews its registration. The revised information must be sent to FDA either electronically or in writing in accordance with paragraph (d) of this section.

[74 FR 2368, Jan. 15, 2009]

Sec. 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed

research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the instituton's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991]

Subpart C--IRB Functions and Operations

Sec. 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

Sec. 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with 50.25. The IRB may require that information, in addition to that specifically mentioned in 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

(f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under 50.24 of this chapter a copy of information that has been publicly disclosed under 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

(h) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that is ongoing on April 30, 2001 are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

[46 FR 8975, Jan. 27, 1981, as amended at 61 FR 51529, Oct. 2, 1996; 66 FR 20599, Apr. 24, 2001]

Sec. 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in theFederal Register,a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in theFederal Register.

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in 56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

Sec. 56.111 Criteria for IRB approval of research

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

(c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 66 FR 20599, Apr. 24, 2001]

Sec. 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Sec. 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

Sec. 56.114 Cooperative research

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D--Records and Reports

Sec. 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by 56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

Subpart E--Administrative Actions for Noncompliance

Sec. 56.120 Lesser administrative actions

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

Sec. 56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest,

such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in theFederal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in 56.123.

Sec. 56.122 Public disclosure of information regarding revocation

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

Sec. 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under 56.121(c).

Sec. 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.
Source: 46 FR 8975, Jan. 27, 1981, unless otherwise noted.

[Code of Federal Regulations]

[Title 21, Volume 5]

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[CITE: 21CFR312]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 312 INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A--General Provisions

Sec. 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

Sec. 312.2 Applicability.

(a)*Applicability.* Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201*et seq* .)).

(b)*Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (*a*) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (*b*) it is shipped in compliance with 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (*a*) blood grouping serum; (*b*) reagent red blood cells; and (*c*) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under 50.24 of this chapter is not exempt from the requirements of this part.

(c)*Bioavailability studies.* The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of 320.31.

(d)*Unlabeled indication.* This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e)*Guidance.* FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

Sec. 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (secs. 201-902, 52 Stat. 1040*et seq* ., as amended (21 U.S.C. 301-392)).

Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

FDA means the Food and Drug Administration.

IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Independent ethics committee (IEC) means a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), as defined in 56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC.

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical investigation (*i.e.* , under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

[52 FR 8831, Mar. 19, 1987, as amended at 64 FR 401, Jan. 5, 1999; 64 FR 56449, Oct. 20, 1999; 73 FR 22815, Apr. 28, 2008]

Sec. 312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

(c) The appropriate FDA Center Director, according to the procedures set forth in 201.26 or 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

[52 FR 8831, Mar. 19, 1987, as amended at 72 FR 73599, Dec. 28, 2007]

Sec. 312.7 Promotion of investigational drugs.

(a)*Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b)*Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c)*Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19476, May 22, 1987; 67 FR 9585, Mar. 4, 2002; 74 FR 40899, Aug. 13, 2009]

Sec. 312.8 Charging for investigational drugs under an IND.

(a)*General criteria for charging* . (1) A sponsor must meet the applicable requirements in paragraph (b) of this section for charging in a clinical trial or paragraph (c) of this section for charging for expanded access to an investigational drug for treatment use under subpart I of this part, except that sponsors need not fulfill the requirements in this section to charge for an approved drug obtained from another entity not affiliated with the sponsor for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, for use of the approved drug as an active control).

(2) A sponsor must justify the amount to be charged in accordance with paragraph (d) of this section.

(3) A sponsor must obtain prior written authorization from FDA to charge for an investigational drug.

(4) FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

(b)*Charging in a clinical trial* --(1)*Charging for a sponsor's drug* . A sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must:

(i) Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

(ii) Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

(iii) Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

(2)*Duration of charging in a clinical trial* . Unless FDA specifies a shorter period, charging may continue for the length of the clinical trial.

(c)*Charging for expanded access to investigational drug for treatment use* . (1) A sponsor who wishes to charge for expanded access to an investigational drug for treatment use under subpart I of this part must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

(2) For expanded access under 312.320 (treatment IND or treatment protocol), such assurance must include:

(i) Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned;

(ii) Evidence of adequate progress in the development of the drug for marketing approval; and

(iii) Information submitted under the general investigational plan (312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(3) The authorization to charge is limited to the number of patients authorized to receive the drug under the treatment use, if there is a limitation.

(4) Unless FDA specifies a shorter period, charging for expanded access to an investigational drug for treatment use under subpart I of this part may continue for 1 year from the time of FDA authorization. A sponsor may request that FDA reauthorize charging for additional periods.

(d)*Costs recoverable when charging for an investigational drug* . (1) A sponsor may recover only the direct costs of making its investigational drug available.

(i) Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

(ii) Indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale) and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

(2) For expanded access to an investigational drug for treatment use under 312.315 (intermediate-size patient populations) and 312.320 (treatment IND or treatment protocol), in addition to the direct costs described in paragraph (d)(1)(i) of this section, a sponsor may recover the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

(3) To support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the calculation is consistent with the requirements of paragraphs (d)(1) and, if applicable, (d)(2) of this section. The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

[74 FR 40899, Aug. 13, 2009]

Sec. 312.10 Waivers.

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:

(1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;

(2) The sponsor's proposed alternative satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9585, Mar. 4, 2002]

Subpart B--Investigational New Drug Application (IND)

Sec. 312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 62 FR 32479, June 16, 1997]

Sec. 312.21 Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are a follows:

(a)*Phase 1.* (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b)*Phase 2.* Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c)*Phase 3.* Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

Sec. 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

Sec. 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1)*Cover sheet (Form FDA-1571).* A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2)*A table of contents.*

(3)*Introductory statement and general investigational plan.* (i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (*a*) The rationale for the drug or the research study; (*b*) the indication(s) to be studied; (*c*) the general approach to be followed in evaluating the drug; (*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (*e*) the estimated number of patients to be given the drug in those studies; and (*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5)*Investigator's brochure.* If required under 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6)*Protocols.* (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation--an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose--and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(*a*) A statement of the objectives and purpose of the study.

(*b*) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(*c*) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(*d*) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(*e*) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(*f*) A description of the observations and measurements to be made to fulfill the objectives of the study.

(*g*) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7)*Chemistry, manufacturing, and control information.* (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(*a*)*Drug substance.* A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy relevant requirements in this paragraph.

(*b*)*Drug product.* A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy certain requirements in this paragraph.

(*c*) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(*d*)*Labeling.* A copy of all labels and labeling to be provided to each investigator.

(*e*)*Environmental analysis requirements.* A claim for categorical exclusion under 25.30 or 25.31 or an environmental assessment under 25.40.

(8)*Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i)*Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii)*Toxicology. (a*) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(*b*) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9)*Previous human experience with the investigational drug.* A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the

subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10)*Additional information.* In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i)*Drug dependence and abuse potential.* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii)*Radioactive drugs.* If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii)*Pediatric studies.* Plans for assessing pediatric safety and effectiveness.

(iv)*Other information.* A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11)*Relevant information.* If requested by FDA, any other relevant information needed for review of the application.

(b)*Information previously submitted.* The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c)*Material in a foreign language.* The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d)*Number of copies.* The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e)*Numbering of IND submissions.* Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

(f)*Identification of exception from informed consent.* If the investigation involves an exception from informed consent under 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in 50.24 of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51529, Oct. 2, 1996; 62 FR 40599, July 29, 1997; 63 FR 66669, Dec. 2, 1998; 65 FR 56479, Sept. 19, 2000; 67 FR 9585, Mar. 4, 2002]

Sec. 312.30 Protocol amendments.

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made. Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

(a)*New protocol.* Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

(b)*Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(*a*) The sponsor has submitted the change to FDA for its review; and

(*b*) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).

(c)*New investigator* . A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under 312.315 or 312.320. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d)*Content and format.* A protocol amendment is required to be prominently identified as such (*i.e.* , "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), and to contain the following:

(1)(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under 312.23(a)(6)(iii)(*b*).

(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e)*When submitted.* A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51530, Oct. 2, 1996; 67 FR 9585, Mar. 4, 2002; 74 FR 40942, Aug. 13, 2009]

Sec. 312.31 Information amendments.

(a)*Requirement for information amendment.* A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) New toxicology, chemistry, or other technical information; or

(2) A report regarding the discontinuance of a clinical investigation.

(b)*Content and format of an information amendment.* An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

(1) A statement of the nature and purpose of the amendment.

(2) An organized submission of the data in a format appropriate for scientific review.

(3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c)*When submitted.* Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 67 FR 9585, Mar. 4, 2002]

Sec. 312.32 IND safety reports.

(a)*Definitions.* The following definitions of terms apply to this section:

Associated with the use of the drug. There is a reasonable possibility that the experience may have been caused by the drug.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred,*i.e.* , it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience : Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience : Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b)*Review of safety information.* The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

(c)*IND safety reports* --(1)*Written reports* --(i) The sponsor shall notify FDA and all participating investigators in a written IND safety report of:

(A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or

(B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents,*i.e.* , "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

(2)*Telephone and facsimile transmission safety reports.* The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

(3)*Reporting format or frequency.* FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the Center for Drug Evaluation and Research or the director of the products review division in the Center for Biologics Evaluation and Research which is responsible for review of the IND.

(4) A sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

(d)*Followup.* (1) The sponsor shall promptly investigate all safety information received by it.

(2) Followup information to a safety report shall be submitted as soon as the relevant information is available.

(3) If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

(4) Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

(e)*Disclaimer.* A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 62 FR 52250, Oct. 7, 1997; 67 FR 9585, Mar. 4, 2002]

Sec. 312.33 Annual reports

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a)*Individual study information.* A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b)*Summary information.* Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 6862, Feb. 11, 1998; 67 FR 9585, Mar. 4, 2002]

Sec. 312.38 Withdrawal of an IND.

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Subpart C--Administrative Actions

Sec. 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

(1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and

(2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:

(1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under 312.42; or

(2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

(1) Thirty days after FDA receives the IND; or

(2) On earlier FDA authorization to ship the drug.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

Sec. 312.41 Comment and advice on an IND.

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under 312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Sec. 312.42 Clinical holds and requests for modification.

(a)*General.* A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b)*Grounds for imposition of clinical hold* --(1)*Clinical hold of a Phase 1 study under an IND.* FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies.

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.* , affecting reproductive organs) or developmental toxicity (*i.e.* , affecting potential offspring). The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2)*Clinical hold of a Phase 2 or 3 study under an IND.* FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(3)*Clinical hold of an expanded access IND or expanded access protocol* . FDA may place an expanded access IND or expanded access protocol on clinical hold under the following conditions:

(i)*Final use* . FDA may place a proposed expanded access IND or treatment use protocol on clinical hold if it is determined that:

(A) The pertinent criteria in subpart I of this part for permitting the expanded access use to begin are not satisfied; or

(B) The expanded access IND or expanded access protocol does not comply with the requirements for expanded access submissions in subpart I of this part.

(ii)*Ongoing use* . FDA may place an ongoing expanded access IND or expanded access protocol on clinical hold if it is determined that the pertinent criteria in subpart I of this part for permitting the expanded access are no longer satisfied.

(4)*Clinical hold of any study that is not designed to be adequate and well-controlled.* FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or

(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in nonconcurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

(5)*Clinical hold of any investigation involving an exception from informed consent under 50.24 of this chapter.* FDA may place a proposed or ongoing investigation involving an exception from informed consent under 50.24 of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) The pertinent criteria in 50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

(6) Clinical hold of any investigation involving an exception from informed consent under 50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under 50.23(d) of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

(c)*Discussion of deficiency.* Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

(d)*Imposition of clinical hold.* The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e)*Resumption of clinical investigations.* An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

(f)*Appeal.* If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with 312.48.

(g)*Conversion of IND on clinical hold to inactive status.* If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under 312.45.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19477, May 22, 1987; 57 FR 13249, Apr. 15, 1992; 61 FR 51530, Oct. 2, 1996; 63 FR 68678, Dec. 14, 1998; 64 FR 54189, Oct. 5, 1999; 65 FR 34971, June 1, 2000; 74 FR 40942, Aug. 13, 2009]

Sec. 312.44 Termination.

(a)*General.* This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in 312.42.

(b)*Grounds for termination* --(1)*Phase 1.* FDA may propose to terminate an IND during Phase 1 if it finds that:

(i) Human subjects would be exposed to an unreasonable and significant risk of illness or unjury.

(ii) The IND does not contain sufficient information required under 312.23 to assess the safety to subjects of the clinical investigations.

(iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.

(iv) The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.

(v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by 312.7.

(vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.

(vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of serious and unexpected adverse experiences in accordance with 312.32 or fails to make any other report required under this part.

(viii) The sponsor fails to submit an accurate annual report of the investigations in accordance with 312.33.

(ix) The sponsor fails to comply with any other applicable requirement of this part, part 50, or part 56.

(x) The IND has remained on inactive status for 5 years or more.

(xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under 312.42(b)(4).

(2)*Phase 2 or 3.* FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or

(ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or

(iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or

(ii) Any of the conditions in 312.42(b)(3) apply.

(c)*Opportunity for sponsor response.* (1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d)*Immediate termination of IND.* Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of whether the IND should be reinstated.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 57 FR 13249, Apr. 15, 1992; 67 FR 9586, Mar. 4, 2002]

Sec. 312.45 Inactive status.

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with 312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under 312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of 312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under 312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under 312.44.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Sec. 312.47 Meetings.

(a)*General.* Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with part 10.

(b)*"End-of-Phase 2" meetings and meetings held before submission of a marketing application.* At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application ("pre-NDA" meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1)*End-of-Phase 2 meetings* --(i)*Purpose.* The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

(ii)*Eligibility for meeting.* While the end-of-Phase 2 meeting is designed primarily for IND's involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii)*Timing.* To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv)*Advance information.* At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the

drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.7 that is publicly available under FDA's public information regulations in part 20.

(v)*Conduct of meeting.* Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA's Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with 10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2)*"Pre-NDA" and "pre-BLA" meetings.* FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

(i) A brief summary of the clinical studies to be submitted in the application.

(ii) A proposed format for organizing the submission, including methods for presenting the data.

(iii) Information on the status of needed or ongoing pediatric studies.

(iv) Any other information for discussion at the meeting.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 63 FR 66669, Dec. 2, 1998; 67 FR 9586, Mar. 4, 2002]

Sec. 312.48 Dispute resolution.

(a)*General.* The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND's as quickly and amicably as possible through the cooperative exchange of information and views.

(b)*Administrative and procedural issues.* When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA's public information regulations in part 20.

(c)*Scientific and medical disputes.* (1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The "end-of-Phase 2" and "pre-NDA" meetings described in 312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may rely on, and may bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.

[52 FR 8831, Mar. 19, 1987, as amended at 55 FR 11580, Mar. 29, 1990]

Subpart D--Responsibilities of Sponsors and Investigators

Sec. 312.50 General responsibilities of sponsors.

Sponsors are responsibile for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

Sec. 312.52 Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

Sec. 312.53 Selecting investigators and monitors.

(a)*Selecting investigators.* A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b)*Control of drug.* A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c)*Obtaining information from the investigator.* Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA-1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(*a*) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(*e*) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 312.64;

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(*g*) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

(2)*Curriculum vitae.* A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3)*Clinical protocol.* (i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

(ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(4)*Financial disclosure information.* Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(d)*Selecting monitors.* A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

Sec. 312.54 Emergency research under 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

[61 FR 51530, Oct. 2, 1996, as amended at 68 FR 24879, May 9, 2003]

Sec. 312.55 Informing investigators.

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in 312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with 312.32.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Sec. 312.56 Review of ongoing investigations.

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Sec. 312.57 Recordkeeping and record retention.

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, 320.38 or 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in 320.38.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 58 FR 25926, Apr. 28, 1993; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

Sec. 312.58 Inspection of sponsor's records and reports.

(a)*FDA inspection.* A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b)*Controlled substances.* If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Sec. 312.59 Disposition of unused supply of investigational drug.

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Sec. 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51530, Oct. 2, 1996]

Sec. 312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

Sec. 312.62 Investigator recordkeeping and record retention.

(a)*Disposition of drug.* An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59.

(b)*Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c)*Record retention.* An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 67 FR 9586, Mar. 4, 2002]

Sec. 312.64 Investigator reports.

(a)*Progress reports.* The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b)*Safety reports.* An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

(c)*Final report.* An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(d)*Financial disclosure reports.* The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

Sec. 312.66 Assurance of IRB review

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes

in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

Sec. 312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

Sec. 312.69 Handling of controlled substances.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Sec. 312.70 Disqualification of a clinical investigator

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

(c) Each IND and each approved application submitted under part 314 containing data reported by an investigator who has been determined to be ineligible to receive investigational drugs will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational drugs solely in compliance with the provisions of this part and of parts 50 and 56.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 62 FR 46876, Sept. 5, 1997; 67 FR 9586, Mar. 4, 2002]

Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Sec. 312.80 Purpose.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

Sec. 312.81 Scope.

This section applies to new drug and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term "life-threatening" means:

(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and

(2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term "severely debilitating" means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

[53 FR 41523, Oct. 21, 1988, as amended at 64 FR 401, Jan. 5, 1999]

Sec. 312.82 Early consultation.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a)*Pre-investigational new drug (IND) meetings.* Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b)*End-of-phase 1 meetings.* When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

[53 FR 41523, Oct. 21, 1988, as amended at 63 FR 66669, Dec. 2, 1998]

Sec. 312.83 Treatment protocols.

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in 312.34 and 312.35. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in 312.42(b)(3)(ii)).

Sec. 312.84 Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in 312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under 312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under 314.101 or part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue a complete response letter under 314.110 of this chapter or the biological product licensing procedures. Such letter, in describing the deficiencies in the application, will address why the results of the research design agreed to under 312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in part 314 or part 600 of this chapter, as well as those in this subpart.

[53 FR 41523, Oct. 21, 1988, as amended at 73 FR 39607, July 10, 2008]

Sec. 312.85 Phase 4 studies.

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

Sec. 312.86 Focused FDA regulatory research.

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

Sec. 312.87 Active monitoring of conduct and evaluation of clinical trials.

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

Sec. 312.88 Safeguards for patient safety.

All of the safeguards incorporated within parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (312.32), safety update reports during agency review of a marketing application (314.50 of this chapter), and postmarketing adverse reaction reporting (314.80 of this chapter).

Subpart F--Miscellaneous

Sec. 312.110 Import and export requirements.

(a)*Imports.* An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under 312.40 and: (1) The consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.

(b)*Exports* . An investigational new drug may be exported from the United States for use in a clinical investigation under any of the following conditions:

(1) An IND is in effect for the drug under 312.40, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator in a study submitted to and allowed to proceed under the IND; or

(2) The drug has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, section 802(b)(1)(A), (f), and (g) of the act, and 1.101 of this chapter; or

(3) The drug is being exported to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or to any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, the applicable provisions of section 802(c), (f), and (g) of the act, and 1.101 of this chapter. Drugs exported under this paragraph that are not the subject of an IND are exempt from the label requirement in 312.6(a); or

(4) Except as provided in paragraph (b)(5) of this section, the person exporting the drug sends a written certification to the Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, at the time the drug is first exported and maintains records documenting compliance with this paragraph. The certification shall describe the drug that is to be exported (*i.e.* , trade name (if any), generic name, and dosage form), identify the country or countries to which the drug is to be exported, and affirm that:

(i) The drug is intended for export;

(ii) The drug is intended for investigational use in a foreign country;

(iii) The drug meets the foreign purchaser's or consignee's specifications;

(iv) The drug is not in conflict with the importing country's laws;

(v) The outer shipping package is labeled to show that the package is intended for export from the United States;

(vi) The drug is not sold or offered for sale in the United States;

(vii) The clinical investigation will be conducted in accordance with 312.120;

(viii) The drug is manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practices;

(ix) The drug is not adulterated within the meaning of section 501(a)(1), (a)(2)(A), (a)(3), (c), or (d) of the act;

(x) The drug does not present an imminent hazard to public health, either in the United States, if the drug were to be reimported, or in the foreign country; and

(xi) The drug is labeled in accordance with the foreign country's laws.

(5) In the event of a national emergency in a foreign country, where the national emergency necessitates exportation of an investigational new drug, the requirements in paragraph (b)(4) of this section apply as follows:

(i)*Situations where the investigational new drug is to be stockpiled in anticipation of a national emergency* . There may be instances where exportation of an investigational new drug is needed so that the drug may be stockpiled and made available for use by the importing country if and when a national emergency arises. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix) of this section, provided that he or she:

(*1*) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who may receive the investigational new drug;

(*2*) Provides a written statement from an authorized official of the importing country's government. The statement must attest that the official agrees with the exporter's statement made under paragraph (b)(5)(i)(A)(*1*) of this section; explain that the drug is to be stockpiled solely for use of the importing country in a national emergency; and describe the potential national emergency that warrants exportation of the investigational new drug under this provision; and

(*3*) Provides a written statement showing that the Secretary of Health and Human Services (the Secretary), or his or her designee, agrees with the findings of the authorized official of the importing country's government. Persons who wish to obtain a written statement from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail:*HHS.SOC@hhs.gov* .

(B) Exportation may not proceed until FDA has authorized exportation of the investigational new drug. FDA may deny authorization if the statements provided under paragraphs (b)(5)(i)(A)(*1*) or (b)(5)(i)(A)(*2*) of this section are inadequate or if exportation is contrary to public health.

(ii)*Situations where the investigational new drug is to be used for a sudden and immediate national emergency* . There may be instances where exportation of an investigational new drug is needed so that the drug may be used in a sudden and immediate national emergency that has developed or is developing. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix), and/or (b)(4)(xi), provided that he or she:

(*1*) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who are expected to receive the investigational new drug and

(*2*) Provides sufficient information from an authorized official of the importing country's government to enable the Secretary, or his or her designee, to decide whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary. Persons who wish to obtain a determination from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail:*HHS.SOC@hhs.gov* .

(B) Exportation may proceed without prior FDA authorization.

(c)*Limitations* . Exportation under paragraph (b) of this section may not occur if:

(1) For drugs exported under paragraph (b)(1) of this section, the IND pertaining to the clinical investigation is no longer in effect;

(2) For drugs exported under paragraph (b)(2) of this section, the requirements in section 802(b)(1), (f), or (g) of the act are no longer met;

(3) For drugs exported under paragraph (b)(3) of this section, the requirements in section 802(c), (f), or (g) of the act are no longer met;

(4) For drugs exported under paragraph (b)(4) of this section, the conditions underlying the certification or the statements submitted under paragraph (b)(5) of this section are no longer met; or

(5) For any investigational new drugs under this section, the drug no longer complies with the laws of the importing country.

(d)*Insulin and antibiotics* . New insulin and antibiotic drug products may be exported for investigational use in accordance with section 801(e)(1) of the act without complying with this section.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 64 FR 401, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002; 70 FR 70729, Nov. 23, 2005]

Sec. 312.120 Foreign clinical studies not conducted under an IND.

(a)*Acceptance of studies.* (1) FDA will accept as support for an IND or application for marketing approval (an application under section 505 of the act or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262)) a well-designed and well-conducted foreign clinical study not conducted under an IND, if the following conditions are met:

(i) The study was conducted in accordance with good clinical practice (GCP). For the purposes of this section, GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study. GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with those described in 50.23 or 50.24(a) of this chapter, or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects; and

(ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

(2) Although FDA will not accept as support for an IND or application for marketing approval a study that does not meet the conditions of paragraph (a)(1) of this section, FDA will examine data from such a study.

(3) Marketing approval of a new drug based solely on foreign clinical data is governed by 314.106 of this chapter.

(b)*Supporting information* . A sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for an IND or application for marketing approval must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601 of this chapter, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1)(i) of this section. The description is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the description must provide either the following information or a cross-reference to another section of the submission where the information is located:

(1) The investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of the components, formulation, specifications, and, if available, bioavailability of the specific drug product used in the clinical study;

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under 314.126 of this chapter;

(6) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in 312.3 of this chapter. The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;

(7) A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion;

(8) A description of how informed consent was obtained;

(9) A description of what incentives, if any, were provided to subjects to participate in the study;

(10) A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistently with the study protocol; and

(11) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1)(i) of this section) and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c)*Waivers* . (1) A sponsor or applicant may ask FDA to waive any applicable requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IND or in an information amendment to an IND, or in an application or in an amendment or supplement to an application submitted under part 314 or 601 of this chapter. A waiver request is required to contain at least one of the following:

(i) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;

(ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(iii) Other information justifying a waiver.

(2) FDA may grant a waiver if it finds that doing so would be in the interest of the public health.

(d)*Records* . A sponsor or applicant must retain the records required by this section for a foreign clinical study not conducted under an IND as follows:

(1) If the study is submitted in support of an application for marketing approval, for 2 years after an agency decision on that application;

(2) If the study is submitted in support of an IND but not an application for marketing approval, for 2 years after the submission of the IND.

[73 FR 22815, Apr. 28, 2008]

Sec. 312.130 Availability for public disclosure of data and information in an IND.

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug will be handled in accordance with the provisions established in 314.430 for the confidentiality of data and information in applications submitted in part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of 601.50 and 601.51.

(c) Notwithstanding the provisions of 314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under 50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, shall submit a request under the Freedom of Information Act.

[52 FR 8831, Mar. 19, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988, as amended at 61 FR 51530, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999; 68 FR 24879, May 9, 2003]

Sec. 312.140 Address for correspondence.

(a) A sponsor must send an initial IND submission to the Center for Drug Evaluation and Research (CDER) or to the Center for Biologics Evaluation and Research (CBER), depending on the Center responsible for regulating the product as follows:

(1)*For drug products regulated by CDER* . Send the IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266; except send an IND submission for an in vivo bioavailability or bioequivalence study in humans to support an abbreviated new drug application to the Office of Generic Drugs (HFD-600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

(2)*For biological products regulated by CDER* . Send the IND submission to the CDER Therapeutic Biological Products Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852.

(3)*For biological products regulated by CBER* . Send the IND submission to the Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

(b) On receiving the IND, the responsible Center will inform the sponsor which one of the divisions in CDER or CBER is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be sent to the appropriate center at the

address indicated in this section and marked to the attention of the responsible division. The outside wrapper of each submission shall state what is contained in the submission, for example, "IND Application", "Protocol Amendment", etc.

(c) All correspondence relating to export of an investigational drug under 312.110(b)(2) shall be submitted to the International Affairs Staff (HFY-50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

[70 FR 14981, Mar. 24, 2005, as amended at 74 FR 13113, Mar. 26, 2009; 74 FR 55771, Oct. 29, 2009; 75 FR 37295, June 29, 2010]

Sec. 312.145 Guidance documents.

(a) FDA has made available guidance documents under 10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain lists of guidance documents that apply to the centers' regulations. The lists are maintained on the Internet and are published annually in theFederal Register.A request for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002. A request for a copy of the CBER list should be directed to the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

[65 FR 56479, Sept. 19, 2000, as amended at 74 FR 13113, Mar. 26, 2009]

Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

Sec. 312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

(a)*Authorization to ship.* (1)(i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.

(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in 312.2(b)(2)(ii) if it is labeled as follows:

CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with 312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b)*Termination of authorization to ship.* FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to part 16.

(c)*Disposition of unused drug.* The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative disposition of unused supplies of the drug provided this alternative disposition does not expose humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988; 67 FR 9586, Mar. 4, 2002]

Subpart H [Reserved]

Subpart I--Expanded Access to Investigational Drugs for Treatment Use

Sec. 312.300 General.

(a)*Scope* . This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b)*Definitions* . The following definitions of terms apply to this subpart:

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or

recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Sec. 312.305 Requirements for all expanded access uses.

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in 312.310 through 312.320.

(a)*Criteria* . FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b)*Submission* . (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:

(i) A cover sheet (Form FDA 1571) meeting the requirements of 312.23(a);

(ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

(iii) The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

(iv) The method of administration of the drug, dose, and duration of therapy;

(v) A description of the facility where the drug will be manufactured;

(vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

(vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

(viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c)*Safeguards* . The responsibilities of sponsors and investigators set forth in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an*investigator* , for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a*sponsor* , for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a*sponsor-investigator* , for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4)*Investigators* . In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of 312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

(5)*Sponsors* . In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by 312.32 and 312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of 312.57. Depending on the type of expanded access, other sponsor responsibilities under subpart D may also apply.

(d)*Beginning treatment* --(1)*INDs* . An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2)*Protocols* . With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in 312.30(a).

(i) Expanded access use under the emergency procedures described in 312.310(d) may begin when the use is authorized by the FDA reviewing official.

(ii) Expanded access use under 312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3)*Clinical holds* . FDA may place any expanded access IND or protocol on clinical hold as described in 312.42.

Sec. 312.310 Individual patients, including for emergency use.

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a)*Criteria* . The criteria in 312.305(a) must be met; and the following determinations must be made:

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(b)*Submission* . The expanded access submission must include information adequate to demonstrate that the criteria in 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of 312.305(b).

(1) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(2) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(3) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c)*Safeguards* . (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under 312.315 or 312.320.

(d)*Emergency procedures* . If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 301-827-1800or 1-800-835-4709, e-mail:*ocod@fda.hhs.gov* . For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail:*druginfo@fda.hhs.gov* . After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail:*emergency.operations@fda.hhs.gov* .

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

[74 FR 40942, Aug. 13, 2009, as amended at 75 FR 32659, June 9, 2010]

Sec. 312.315 Intermediate-size patient populations.

Under this section, FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

(a)*Need for expanded access* . Expanded access under this section may be needed in the following situations:

(1)*Drug not being developed* . The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.

(2)*Drug being developed* . The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.

(3)*Approved or related drug* . (i) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or

(ii) The drug contains the same active moiety as an approved drug product that is unavailable through marketing due to failure to meet the conditions of the approved application or a drug shortage.

(b)*Criteria* . The criteria in 312.305(a) must be met; and FDA must determine that:

(1) There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and

(2) There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.

(c)*Submission* . The expanded access submission must include information adequate to satisfy FDA that the criteria in 312.305(a) and paragraph (b) of this section have been met. The expanded access submission must meet the requirements of 312.305(b). In addition:

(1) The expanded access submission must state whether the drug is being developed or is not being developed and describe the patient population to be treated.

(2) If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.

(3) If the drug is being studied in a clinical trial, the sponsor must explain why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.

(d)*Safeguards* . (1) Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section.

(i) If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use.

(ii) If the drug is being actively developed, FDA will consider whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug.

(iii) As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under 312.320.

(2) The sponsor is responsible for monitoring the expanded access protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

Sec. 312.320 Treatment IND or treatment protocol.

Under this section, FDA may permit an investigational drug to be used for widespread treatment use.

(a)*Criteria* . The criteria in 312.305(a) must be met, and FDA must determine that:

(1)*Trial status* . (i) The drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or

(ii) All clinical trials of the drug have been completed; and

(2)*Marketing status* . The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and

(3)*Evidence* . (i) When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or

(ii) When the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence.

(b)*Submission* . The expanded access submission must include information adequate to satisfy FDA that the criteria in 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of 312.305(b).

(c)*Safeguard* . The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.
Source: 52 FR 8831, Mar. 19, 1987, unless otherwise noted

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=314)

Subpart B--Applications

Sec. 314.80 Postmarketing reporting of adverse drug experiences

(a)*Definitions.* The following definitions of terms apply to this section:

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience. Any adverse drug experience that places the patient, in the view of the initial reporter, a*timmediate* risk of death from the adverse drug experience as it occurred,*i.e.* , it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

Serious adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected adverse drug experience. Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (*i.e.* , included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

(b)*Review of adverse drug experiences.* Each applicant having an approved application under 314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

(c)*Reporting requirements.* The applicant shall report to FDA adverse drug experience information, as described in this section. The applicant shall submit two copies of each report described in this section to the Central Document Room, 5901-B Ammendale Rd., Beltsville, MD 20705-1266. FDA may waive the requirement for the second copy in appropriate instances.

(1)(i)*Postmarketing 15-day "Alert reports".* The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

(ii)*Postmarketing 15-day "Alert reports"--followup.* The applicant shall promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information. Postmarketing 15-day Alert reports and followups to them shall be submitted under separate cover.

(iii)*Submission of reports.* The requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section, concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person other than the applicant (nonapplicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor. To avoid unnecessary duplication in the submission to FDA of reports required by paragraphs (c)(1)(i) and (c)(1)(ii) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. If a nonapplicant elects to submit adverse drug experience reports to the applicant rather than to FDA, the nonapplicant shall submit each report to the applicant within 5 calendar days of receipt of the report by the nonapplicant, and the applicant shall then comply with the requirements of this section. Under this circumstance, the nonapplicant shall maintain a record of this action which shall include:

(A) A copy of each adverse drug experience report;

(B) The date the report was received by the nonapplicant;

(C) The date the report was submitted to the applicant; and

(D) The name and address of the applicant.

(iv)*Report identification.* Each report submitted under this paragraph shall bear prominent identification as to its contents,*i.e.* , "15-day Alert report," or "15-day Alert report-followup."

(2)*Periodic adverse drug experience reports.* (i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals. The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

(ii) Each periodic report is required to contain: (*a*) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification number, adverse reaction term(s), and date of submission to FDA); (*b*) a FDA Form 3500A (Adverse Reaction Report) for each adverse drug experience not reported under paragraph (c)(1)(i) of this section (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and (*c*) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).

(iii) Periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application), from reports in the scientific literature, and from foreign marketing experience.

(d)*Scientific literature.* (1) A 15-day Alert report based on information from the scientific literature is required to be accompanied by a copy of the published article. The 15-day reporting requirements in paragraph (c)(1)(i) of this section (*i.e.* , serious, unexpected adverse drug experiences) apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial.

(2) As with all reports submitted under paragraph (c)(1)(i) of this section, reports based on the scientific literature shall be submitted on FDA Form 3500A or comparable format as prescribed by paragraph (f) of this section. In cases where the applicant believes that preparing the FDA Form 3500A constitutes an undue hardship, the applicant may arrange with the Office of Surveillance and Epidemiology for an acceptable alternative reporting format.

(e)*Postmarketing studies.* (1) An applicant is not required to submit a 15-day Alert report under paragraph (c) of this section for an adverse drug experience obtained from a postmarketing study (whether or not conducted under an investigational new drug application) unless the applicant concludes that there is a reasonable possibility that the drug caused the adverse experience.

(2) The applicant shall separate and clearly mark reports of adverse drug experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the applicant.

(f)*Reporting FDA Form 3500A.* (1) Except as provided in paragraph (f)(3) of this section, the applicant shall complete FDA Form 3500A for each report of an adverse drug experience (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form).

(2) Each completed FDA Form 3500A should refer only to an individual patient or a single attached publication.

(3) Instead of using FDA Form 3500A, an applicant may use a computer-generated FDA Form 3500A or other alternative format (e.g., a computer-generated tape or tabular listing) provided that:

(i) The content of the alternative format is equivalent in all elements of information to those specified in FDA Form 3500A; and

(ii) The format is agreed to in advance by the Office of Surveillance and Epidemiology.

(4) FDA Form 3500A and instructions for completing the form are available on the Internet at*http://www.fda.gov/medwatch/index.html* .

(g)*Multiple reports.* An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(h)*Patient privacy.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code number to each report, preferably not more than eight characters in length. The applicant should include the name of the reporter from whom the information was received. Names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20.

(i)*Recordkeeping.* The applicant shall maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(j)*Withdrawal of approval.* If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(k)*Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. For purposes of this provision, the term "applicant" also includes any person reporting under paragraph (c)(1)(iii) of this section.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 51 FR 24481, July 3, 1986; 52 FR 37936, Oct. 13, 1987; 55 FR 11580, Mar. 29, 1990; 57 FR 17983, Apr. 28, 1992; 62 FR 34168, June 25, 1997; 62 FR 52251, Oct. 7, 1997; 63 FR 14611, Mar. 26, 1998; 67 FR 9586, Mar. 4, 2002; 69 FR 13473, Mar. 23, 2004; 74 FR 13113, Mar. 26, 2009]

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=314)

Subpart B--Applications

Sec. 314.81 Other postmarketing reports.

(a)*Applicability.* Each applicant shall make the reports for each of its approved applications and abbreviated applications required under this section and section 505(k) of the act.

(b)*Reporting requirements.* The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1)*NDA--Field alert report.* The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA--Field Alert Report."

(i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

(2)*Annual report.* The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

(i)*Summary.* A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(ii)(*a*)*Distribution data.* Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(*b*)*Authorized generic drugs* . If applicable, the date each authorized generic drug (as defined in 314.3) entered the market, the date each authorized generic drug ceased being distributed, and the corresponding trade or brand name. Each dosage form and/or strength is a different authorized generic drug and should be listed separately. The first annual report submitted on or after January 25, 2010 must include the information listed in this paragraph for any authorized generic drug that was marketed during the time period covered by an annual report submitted after January 1, 1999. If information is included in the annual report with respect to any authorized generic drug, a copy of that portion of the annual report must be sent to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drug Quality Assessment, Bldg. 21, rm. 2562, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, and marked "Authorized Generic Submission" or, by e-mail, to the Authorized Generics electronic mailbox at*AuthorizedGenerics@fda.hhs.gov* with "Authorized Generic Submission" indicated in the subject line. However, at such time that FDA has required that annual reports be submitted in an electronic format, the information required by this paragraph must be submitted as part of the annual report, in the electronic format specified for submission of annual reports at that time, and not as a separate submission under the preceding sentence in this paragraph.

(iii)*Labeling.* (*a*) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(*b*) The content of labeling required under 201.100(d)(3) of this chapter (*i.e.* , the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format. Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of 11.10(a), (c) through (h), and (k), and the corresponding requirements of 11.30.

(*c*) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

(iv)*Chemistry, manufacturing, and controls changes.* (*a*) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(*b*) A full description of the manufacturing and controls changes not requiring a supplemental application under 314.70 (b) and (c), listed by date in the order in which they were implemented.

(v)*Nonclinical laboratory studies.* Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi)*Clinical data.* (*a*) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(*b*) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(*c*) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii)*Status reports of postmarketing study commitments.* A status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or that the applicant has committed, in writing, to conduct either at the time of approval of an application for the drug product or a supplement to an application, or after approval of the application or a supplement. For pediatric studies, the status report shall include a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under 201.23 of this chapter. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(*a*)*Content of status report.* The following information must be provided for each postmarketing study reported under this paragraph:

(*1*)*Applicant's name.*

(*2*)*Product name.* Include the approved drug product's established name and proprietary name, if any.

(*3*)*NDA, ANDA, and supplement number.*

(*4*)*Date of U.S. approval of NDA or ANDA.*

(*5*)*Date of postmarketing study commitment.*

(*6*)*Description of postmarketing study commitment.* The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

(*7*)*Schedule for completion and reporting of the postmarketing study commitment.* The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.

(*8*)*Current status of the postmarketing study commitment.* The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:

(*i*)*Pending.* The study has not been initiated, but does not meet the criterion for delayed.

(*ii*)*Ongoing.* The study is proceeding according to or ahead of the original schedule described under paragraph (b)(2)(vii)(*a*)(*7*) of this section.

(*iii*)*Delayed.* The study is behind the original schedule described under paragraph (b)(2)(vii)(*a*)(*7*) of this section.

(*iv*)*Terminated.* The study was ended before completion but a final study report has not been submitted to FDA.

(*v*)*Submitted.* The study has been completed or terminated and a final study report has been submitted to FDA.

(*9*)*Explanation of the study's status.* Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(2)(vii)(*a*)(*8*) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(2)(vii)(*a*)(*7*) of this section has changed since the last report.

(*b*)*Public disclosure of information.* Except for the information described in this paragraph, FDA may publicly disclose any information described in paragraph (b)(2)(vii) of this section, concerning a postmarketing study, if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in 20.61 of this chapter, or information, described in 20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(viii)*Status of other postmarketing studies.* A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

(ix)*Log of outstanding regulatory business.* To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the agency, a list of the agency's unanswered correspondence with the applicant).

(3)*Other reporting* --(i)*Advertisements and promotional labeling.* The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 is available on the Internet at*http://www.fda.gov/opacom/morechoices/fdaforms/cder.html* .

(ii)*Special reports.* Upon written request the agency may require that the applicant submit the reports under this section at different times than those stated.

(iii)*Notification of discontinuance* . (*a*) An applicant who is the sole manufacturer of an approved drug product must notify FDA in writing at least 6 months prior to discontinuing manufacture of the drug product if:

(*1*) The drug product is life supporting, life sustaining, or intended for use in the prevention of a serious disease or condition; and

(*2*) The drug product was not originally derived from human tissue and replaced by a recombinant product.

(*b*) For drugs regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER), one copy of the notification required by paragraph (b)(3)(iii)(*a*) of this section must be sent to the CDER Drug Shortage Coordinator, at the address of the Director of CDER; one copy to the CDER Drug Registration and Listing Team, Division of Compliance Risk Management and Surveillance; and one copy to either the director of the review division in CDER that is responsible for reviewing the application, or the director of the office in CBER that is responsible for reviewing the application.

(*c*) FDA will publicly disclose a list of all drug products to be discontinued under paragraph (b)(3)(iii)(*a*) of this section. If the notification period is reduced under 314.91, the list will state the reason(s) for such reduction and the anticipated date that manufacturing will cease.

(iv)*Withdrawal of approved drug product from sale.* (*a*) The applicant shall submit on Form FDA 2657 (Drug Product Listing), within 15 working days of the withdrawal from sale of a drug product, the following information:

(*1*) The National Drug Code (NDC) number.

(*2*) The identity of the drug product by established name and by proprietary name.

(*3*) The new drug application or abbreviated application number.

(*4*) The date of withdrawal from sale. It is requested but not required that the reason for withdrawal of the drug product from sale be included with the information.

(*b*) The applicant shall submit each Form FDA-2657 to the Records Repository Team (HFD-143), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(*c*) Reporting under paragraph (b)(3)(iv) of this section constitutes compliance with the requirements under 207.30(a) of this chapter to report "at the discretion of the registrant when the change occurs."

(c)*General requirements* --(1)*Multiple applications.* For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

(2)*Patient identification.* Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe that the reports do not represent actual results obtained.

(d)*Withdrawal of approval.* If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 57 FR 17983, Apr. 28, 1992; 63 FR 66670, Dec. 2, 1998; 64 FR 401, Jan. 5, 1999; 65 FR 64617, Oct. 30, 2000; 66 FR 10815, Feb. 20, 2001; 68 FR 69019, Dec. 11, 2003; 69 FR 18766, Apr. 8, 2004; 69 FR 48775, Aug. 11, 2004; 72 FR 58999, Oct. 18, 2007; 74 FR 13113, Mar. 26, 2009; 74 FR 37167, July 28, 2009]

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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

PART 314 -- APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=314)

Subpart D--FDA Action on Applications and Abbreviated Applications

Sec. 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i)*Placebo concurrent control.* The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

(ii)*Dose-comparison concurrent control.* At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii)*No treatment concurrent control.* Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv)*Active treatment concurrent control.* The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v)*Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drug Evaluation and Research may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 64 FR 402, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002]

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Caton, John Jr., M.D. 8/26/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 11-HFD-45-08-02

John Caton, Jr., M.D.
Willamette Valley Cancer Institute
3377 Riverbend Drive, Suite 500
Springfield, OR 97477-8802

Dear Dr. Caton:

Between August 2 and August 20, 2010, Heika R. Tait, representing the U.S. Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol **(b)(4)**, titled "**(b)(4)**") of the investigational drugs **(b)(4)** and **(b)(4)** performed for **(b)(4)**.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your September 10, 2010, written response to the Form FDA 483 ("written response"), we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Heika R. Tait presented and discussed with you Form FDA 483, Inspectional Observations.

We wish to emphasize the following:

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. Examples of your failure to follow the investigational plan include, but are not limited to, the following:

a. Section 3 of the protocol specified that subjects be randomized to receive either **(b)(4)** or **(b)(4)**. However, according to your November 2, 2009, report to the Institutional Review Board (IRB), Subject 6002 received a combination of the investigational drugs **(b)(4)** and **(b)(4)** on July 29, 2009, even though this subject, one of only two enrolled at your site, was randomized to receive only **(b)(4)**. In addition, according to an October 20, 2009, letter from the sponsor addressed to you, analyses of post-infusion blood samples for Subject 6002 indicated the presence of both **(b)(4)** and **(b)(4)**.

b. Section 9.2 of the protocol specified that records of adverse events must have certain adverse event attributes assigned by the investigator, including, but not limited to, the following: event description (with detail appropriate to the event); and assessment of relatedness to investigational product (IP), chemotherapy, or the combination of IP and chemotherapy.

These attributes were not recorded in the adverse events log for Subject 6002.

Failure to randomize subjects properly and to capture adverse event attributes raises concerns about the extent to which subjects' rights, safety, and welfare were protected, and also raises concerns about the reliability of the data at your site. Your written response states generally that you will conduct research studies "under the umbrella of US Oncology Research going forward as there are checks and balances in place" to prevent a recurrence of the violations cited in this letter, and includes new Standard Operating Procedures (SOPs) for drug accountability. However, as the clinical investigator, it was your responsibility to ensure that the study was conducted in accordance with the investigational plan; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

2. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

a. The Return of Investigation Product for Destruction Form indicates that 4 vials of investigational product (**(b)(4)**) were missing. You have no records to account for the disposition of these vials.

b. During the inspection, you and your staff informed Investigator Tait that the investigational drugs were stored at one office, and were transported to another office, where the subjects received the drugs. However, there are no records to document this transfer of the investigational drugs.

c. The protocol required that an IP Accountability and Preparation Record be kept current, and that it contain specific information, including the dates and quantity of the investigational drug dispensed. It appears that you did not maintain any investigational drug accountability records with respect to the dispensing of **(b)(4)** and **(b)(4)**. The dates and quantity of investigational drug used for each subject were not documented.

Failure to maintain adequate drug disposition records raises concerns about subject safety and data integrity. We acknowledge that your written response states that upon your discovery of both the lack of drug accountability and the missing vials, pharmacy and research SOPs were evaluated and revised; and that future studies at your site will be conducted under the umbrella of US Oncology Research, which has an electronic drug accountability system. However, as the clinical investigator, it was your responsibility to ensure that adequate records of the disposition of the drug were maintained; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

3. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].

a. Subject 6002 was admitted to the hospital for bilateral deep venous thrombosis (DVT) and pulmonary embolism on **(b)(4)** and was discharged on **(b)(4)**. You did not report this hospitalization to the IRB until 11/2/09.

b. Subject 6002 expired on **(b)(4)**, and you did not report this death to the IRB until 11/4/09.

Failure to report to the IRB unanticipated problems involving risks to subjects raises concerns about subject safety by undermining the IRB's role in continuing review and evaluating risks to subjects. We acknowledge that your written response states that future studies at your site will be conducted under the umbrella of US Oncology Research, and that with all US Oncology Research studies, unanticipated problems are reported to a project manager or safety specialist, who in turn reports the problem to the IRB. However, as the clinical investigator, it was your responsibility to ensure that unanticipated problems involving risks to human subjects or others were promptly reported to the IRB; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

Your general responsibilities as a clinical investigator include obtaining the informed consent of each human subject to whom the drug is administered, in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60]. 21 CFR 50.27 requires that informed consent be documented by the use of a written consent form approved by the IRB. However, on July 10, 2009, Subject 6002 signed an informed consent form that appears to be an informed consent template that was not approved by the IRB. At the top of each page of the form signed by Subject 6002, the form states, "Approvable Template MUST BE APPROVED FOR SITES BEFORE USE AS MODIFIED Oct 02, 2008." The IRB's May 12, 2009, Certificate of Approval for Protocol **(b)(4)** directed you, as the clinical investigator, to "[u]se only the most current consent form bearing the [IRB] 'APPROVED' stamp." Because the informed consent form signed by Subject 6002 did not bear this "APPROVED" stamp, and instead indicated that it was a template form not yet approved by the IRB, it appears that Subject 6002's informed consent was not documented by the use of a written consent form approved by the IRB.

Failure to obtain informed consent in accordance with the provisions of 21 CFR part 50 raises concerns about the extent to which subjects' rights, safety, and welfare were protected. We acknowledge that your written response states that future studies at your site will be conducted under the umbrella of US Oncology Research, and that the Clinical Trials Management System provided by US Oncology Research studies will only allow staff to print the most current informed consent form. Your response also states that all Clinical Research Coordinators will only print the informed consent form as needed for each patient from the Clinical Trials Management System, to ensure that the most up-to-date informed consent form is used. However, as the clinical investigator, it was your responsibility to ensure that informed consent was obtained in accordance with the provisions of 21 CFR part 50; and US Oncology Research's policies, procedures, and activities do not negate your responsibility as the clinical investigator.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future.

Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity (formerly Lewin), M.D., M.P.H.
Branch Chief
Good Clinical Practice Enforcement Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Acting Office Director

Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLIE K BALL
08/26/2011

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FR DATE: 11/06/2002

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[Notices]
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From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr06no02-79]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N-1526]

Robert A. Fiddes; Debarment Order

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order under the Federal Food, Drug, and Cosmetic Act (the act) debarring Dr. Robert A. Fiddes for 20 years from providing services in any capacity to a person that has an approved or pending drug product application. FDA bases this order on a finding that Dr. Fiddes was convicted of a felony under Federal law for conspiring to make false statements to a government agency, and was a material participant in offenses for which three other people are being debarred. Dr. Fiddes has failed to request a hearing and, therefore, has waived his opportunity for a hearing concerning this action.

DATES: This order is effective November 6, 2002.

ADDRESSES: Submit applications for termination of debarment to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm., 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Mary Catchings, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

On September 30, 1997, the U.S. District Court for the Central District of California accepted Dr. Fiddes' plea and entered judgment against him for one count of conspiring to make false statements to a government agency, the FDA, in violation of 18 U.S.C. 371 and 1001. This conspiracy conviction was based on Dr. Fiddes participating in, directing, and encouraging the submission of false information to sponsors in required reports for clinical studies used by FDA to evaluate the safety and effectiveness of drug products.

As a result of this conviction, FDA served Dr. Fiddes by certified mail on June 6, 2002, a notice proposing to debar him for 20 years from providing services in any capacity to a person that has an approved or pending drug product application. The proposal also offered Dr. Fiddes an opportunity for a hearing on the proposal. The debarment proposal was based on findings: (1) Under section 306(b)(2)(B)(i)(II) of the act (21 U.S.C. 335a(b)(2)(B)(i)(II)) that Dr. Fiddes was convicted of a felony under Federal law for conspiracy to make false statements to a government agency and, (2) under section 306(b)(2)(B)(iii) of the act that Dr. Fiddes was a material participant in offenses leading to the conviction and debarment of three other individuals. Dr. Fiddes was provided 30 days to file objections and to request a hearing. Dr. Fiddes did not request a hearing. His failure to request a hearing

constitutes a waiver of his opportunity for a hearing and a waiver of any contentions concerning his debarment.

II. Findings and Order

Therefore, the Director, Center for Drug Evaluation and Research, under section 306(b)(2)(B) of the act, and under authority delegated to her (21 CFR 5.99), finds that Dr. Robert A. Fiddes: (1) Has been convicted of a felony under Federal law for conspiring to make false statements to a government agency, and (2) was a material participant in offenses leading to the conviction and debarment of three other individuals.

As a result of the foregoing findings, Dr. Robert A. Fiddes is debarred for 20 years (4 periods of 5 years, to run consecutively, based on his conviction of a Federal felony and his role as a material participant in the offenses leading to the conviction and debarment of three other individuals) from providing services in any capacity to a person that has an approved or pending drug product application under section 505, 512, or 802 of the act (21 U.S.C. 355, 360b, or 382), or under section 351 of the Public Health Service Act (42 U.S.C. 262) (see sections 306(c)(1)(B) and (c)(2)(A)(iii) and 201(dd) of the act (21 U.S.C. 321(dd))). Any person with an approved or pending drug product application who knowingly uses the services of Dr. Fiddes, in any capacity, during his period of debarment, will be subject to civil money penalties. If Dr. Fiddes, during his period of debarment, provides services in any capacity to a person with an approved or pending drug product application, he will be subject to civil money penalties. In addition, FDA will not accept or review any abbreviated new drug applications submitted by or with the assistance of Dr. Fiddes during his period of debarment.

Any application by Dr. Fiddes for termination of debarment under section 306(d)(4) of the act should be identified with Docket No. 00N-1526 and sent to the Dockets Management Branch (see ADDRESSES). All such submissions are to be **filed** in four copies. The public availability of information in these submissions is governed by 21 CFR 10.20(j). Publicly available submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 15, 2002.
Janet Woodcock,
Director, Center for Drug Evaluation and Research.
[FR Doc. **02**-**28256** **Filed** 11-5-**02**; 8:45 am]
BILLING CODE 4160-01-S

Links on this page:

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Deputy Attorney General
California Department of Justice
300 South Spring Street, Suite 5212
Los Angeles, California 90013-1233
Telephone: (213) 897-2555

Attorneys for Complainant

BEFORE THE
DIVISION OF MEDICAL QUALITY
MEDICAL BOARD OF CALIFORNIA
DEPARTMENT OF CONSUMER AFFAIRS
STATE OF CALIFORNIA

In the Matter of the Accusation Against: **ROBERT ALAN FIDDES, M.D.** 12291 E. Washington Boulevard Suite No. 106 Whittier, California 90606 Physician's and Surgeon's Certificate No. A-24377, Respondent.	Case No. 11-97-79246 **DEFAULT DECISION** (Gov't Code § 11520)

The above-captioned matter came on regularly before the Division of Medical Quality ("Division"), Medical Board of California ("Board"), Department of Consumer Affairs, State of California, for action as a default matter.

FINDINGS OF FACT

The Division, having reviewed the pleadings, documents of service, affidavits, admissions of the respondent, and other evidence, finds that:

Jurisdiction

1. On August 18, 1971, the Board issued Physician's and Surgeon's Certificate No. A-24377 to Robert Alan Fiddes, M.D. ("respondent"). Said certificate expired on March 31, 1999, and has not been renewed. The Division retains jurisdiction to take disciplinary action against respondent's certificate pursuant to Business and Professions Code section 118.

2. On June 26, 1998, Complainant Ron Joseph, in his official capacity as Executive Director of the Board, filed with the Division an Accusation bearing Board Case No. 11-97-79246. Said Accusation is now pending against Robert Alan Fiddes, M.D., the respondent named therein.

3. At all times relevant hereto, and currently, respondent's address of record on file with the Board was and is 12291 E. Washington Boulevard, No. 106, Whittier, California 90606. Section 1303 of Title 16 of the California Code of Regulations requires licensees of the Board to maintain at all times a current address of record with the Board. (See also, Business and Professions Code section 136, subdivision (a).)

4. In accordance with section 11505, subdivision (c), of the Government Code, on June 26, 1998, Arlene Krysinski, an employee of the Board, sent by certified mail a package containing a copy of the Accusation on file in Board Case No. 11-97-79246, along with a Statement to Respondent, a copy of Government Code sections 11507.5 et seq., Notice of Defense forms, and other materials, to respondent's address of record, to wit, 12291 E. Washington Boulevard, No. 106, Whittier, California

90606. On or about August 10, 1998, the above-described package of materials was returned to the Board by the U.S. Postal Service with a forwarding address noted thereon, to wit: 1413 Via Davalos, Palos Verdes Estates, California 90274-1943. Ms. Krysinski performed computerized database research which indicated that said address was an address used by respondent.

5. On August 17, 1998, Ms. Krysinski re-sent the above-described package via certified mail to respondent's address in Palos Verdes Estates. Said package subsequently was returned to the Board by the U.S. Postal Service, with the following U.S.P.S. notations thereon: "unclaimed" and "refused."

6. On October 8, 1998, Ms. Krysinski re-sent two copies of the above-described Accusation package, this time via first class mail, to both respondent's address of record and respondent's address in Palos Verdes Estates. Neither package was returned to the Board by the U.S. Postal Service.

7. In a further effort to serve respondent, on October 21, 1998, Ms. Krysinski sent via first class mail another copy of the Accusation package to Brian Sun, Esq., respondent's attorney of record in the criminal action (U.S. v. Robert A. Fiddes, U.S. District Court, Central District of California, Case No. CR-97-927) referenced in the instant Accusation. Said Accusation package was not returned to the Board by the U.S. Post Office.

8. In a final effort to serve respondent, Ms. Krysinski determined respondent's whereabouts and serial number in the federal prison system (Metropolitan Detention Center; prisoner no. 12574-112) and on November 25, 1998, sent to respondent via certified mail another copy of the above-described Accusation package. On December 4, 1998, the Board received the green certified mail return receipt which accompanied the Metropolitan Detention Center mailing. It was signed with what appeared to be three initials ("R _ F") and reflected a delivery date of November 30, 1998.

9. Copies of the Accusation, relevant accompanying documents, the declarations of service for the above-described efforts to effect service of process, and the aforementioned green certified mail return receipt are attached hereto, collectively, as **"Exhibit 1,"** and are incorporated herein by reference.

10. The Accusation package envelope which was marked by the U.S. Post Office with a forwarding address and returned to the Board (see paragraph 4, supra), and the Accusation package envelope which was marked "unclaimed" and "refused," and returned to the Board (see paragraph 5, supra), are attached hereto, collectively, as **"Exhibit 2"** and incorporated herein by this reference.

Default

11. Government Code section 11506 provides, in pertinent part, that:

"(c) The respondent shall be entitled to a hearing on the merits if the respondent files a notice of defense, and the notice shall be deemed a specific denial of all parts of the accusation not expressly admitted. Failure to file a notice of defense shall constitute a waiver of respondent's right to a hearing, but the agency in its discretion may nevertheless grant a hearing. . . ."

12. Respondent failed to file timely, and to date has not filed, a Notice of Defense in this matter. Respondent therefore is in default and has waived his right to a hearing on the merits of the Accusation on file in Board Case No. 11-97-79246.

13. Government Code section 11520 states, in relevant portion, that:

"(a) If the respondent either fails to file a notice of defense or to appear at the hearing, the agency may take action based upon the respondent's express admissions or upon other evidence and affidavits may be used as evidence without any notice to respondent; . . ."

14. Pursuant to its authority under Government Code section 11520, the Division will take action based upon respondent's express admissions and other evidence, without further hearing.

Allegations

15. The factual allegations set forth in the Accusation are matters of public record and are hereby officially noticed by the Division of Medical Quality, in accordance with Government Code section 11515.

16. The factual allegations, and each of them, contained in the Accusation on file in Board Case No. 11-97-79246 are true.

DETERMINATION OF ISSUES

Jurisdiction

1. Respondent was properly served with the Accusation on file herein and was given due notice of the charges in said Accusation. Respondent has failed to file a Notice of Defense.

2. The Division has jurisdiction over respondent and may proceed to adjudicate this matter by way of default.

Causes for License Discipline

3. By reason of the Findings of Fact set forth above, jointly and severally, respondent's Physician's and Surgeon's Certificate is subject to disciplinary action due to his conviction of a substantially related crime, with attendant circumstances, which is unprofessional conduct under Business and Professions Code sections 2236, 2234, subdivision (e), 2261, 2262, and which is independent grounds for license discipline pursuant to Business and Professions Code section 490.

4. By reason of Determination of Issues No. 3, supra, and pursuant to sections 2220, 2227, 2234, 490 of the Business and Professions Code, the Division is authorized to revoke respondent's Physician's and Surgeon's Certificate for each and every act of unprofessional conduct listed above, jointly and severally.

Wherefore, the Division of Medical Quality, Medical Board of California, Department of Consumer Affairs, State of California, makes the following decision and order:

DECISION AND ORDER OF THE
DIVISION OF MEDICAL QUALITY
MEDICAL BOARD OF CALIFORNIA

Physician's and Surgeon's Certificate No. A-24377, heretofore issued to respondent Robert Alan Fiddes, M.D., is hereby revoked.

An effective date of **March 15,** , 2000, has been assigned to this Order.

Pursuant to Government Code section 11520, subdivision (c), respondent may serve a written motion requesting that the decision be vacated and stating the grounds relied on within seven (7) days after service of the decision on respondent. The agency in its discretion may vacate the decision and grant a hearing on a showing of good cause, as defined in the statute.

Made this **14th** day of **February**, 2000.

FOR THE DIVISION OF MEDICAL QUALITY
MEDICAL BOARD OF CALIFORNIA
Ira Lubell, M.D., Chair, Panel A

EXHIBIT "1"

DANIEL E. LUNGREN
Attorney General of the State of California
ELISA B. WOLFE [State Bar No. 120357]
Deputy Attorney General
California Department of Justice
300 South Spring Street, Suite 5212
Los Angeles, California 90013-1233
Telephone: (213) 897-2555

Attorneys for Complainant

BEFORE THE
DIVISION OF MEDICAL QUALITY
MEDICAL BOARD OF CALIFORNIA
DEPARTMENT OF CONSUMER AFFAIRS
STATE OF CALIFORNIA

In the Matter of the Accusation Against: **ROBERT ALAN FIDDES, M.D.** 12291 E. Washington Blvd., No. 106 Whittier, California 90606 Physician's and Surgeon's Certificate No. A 24377 Respondent.	Case No. 11-97-79246 **ACCUSATION**

Ron Joseph ("Complainant"), for causes for license discipline, alleges:

PARTIES

1. Complainant brings this accusation solely in his official capacity as the Executive Director of the Medical Board of California (hereinafter the "Board").

2. On or about August 18, 1971, the Board issued Physician's and Surgeon's Certificate No. A24377 to Robert Alan Fiddes, M.D. (hereinafter "respondent"). At all times relevant

to the charges brought herein, this license has been in full force and effect. Unless renewed, it will expire on March 31, 1999.

3. On or about January 2, 1991, respondent was issued Physician Assistant Supervisor Approval No. SA 18798. Said approval expired on March 31, 1997, and has not been renewed since the date it expired.

JURISDICTION AND LEGAL AUTHORITY

4. This accusation is brought before the Division of Medical Quality (hereinafter the "Division") of the Board, under the authority of the following sections of the Business and Professions Code.

5. Business and Professions Code section 2220 requires that the Division of Medical Quality of the Medical Board of California shall enforce and administer the provisions of Article 12[1] of the Medical Practice Act[2] as to all holders of physician's and surgeon's certificates.

6. Business and Professions Code section 2227 provides that the Division may revoke, suspend for a period not to exceed one year, or place on probation and require payment of probation costs, or impose other discipline upon the physician's and surgeon's certificate of any licensee who has been found guilty under the Medical Practice Act.

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1. Bus. and Prof. Code §§ 2220-2319.

2. Bus. and Prof. Code § 2000 et seq.

7. Business and Professions Code section 2234 states in relevant part that:

"The Division of Medical Quality shall take action against any licensee who is charged with unprofessional conduct. In addition to other provisions of this article, unprofessional conduct **includes, but is not limited to**, the following:

"(a) Violating or attempting to violate, directly or indirectly, or assisting in or abetting the violation of, or conspiring to violate, any provision of this chapter.

"(b) Gross negligence.

"(c) Repeated negligent acts.

"(d) Incompetence.

"(e) The commission of any act involving dishonesty or corruption which is substantially related to the qualifications, functions, or duties of a physician and surgeon...." [emphasis added.]

8. Business and Professions Code section 2236 provides in pertinent portion that:

"(a) The conviction of any offense substantially related to the qualifications, functions, or duties of a physician and surgeon constitutes unprofessional conduct within the meaning of this chapter. The record of conviction shall be conclusive evidence only of the fact that the conviction occurred.

...

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"(c) ... The division may inquire into the circumstances surrounding the commission of a crime in order to fix the degree of discipline or to determine if the conviction is of an offense substantially related to the qualifications, functions, or duties of a physician and surgeon.

"(d) A plea or verdict of guilty or a conviction after a plea of nolo contendere is deemed to be a conviction within the meaning of this section and Section 2236.1. The record of conviction shall be conclusive evidence of the fact that the conviction occurred."

9. Business and Professions Code section 490 declares that:

"A board may suspend or revoke a license on the ground that the licensee has been convicted of a crime, if the crime is substantially related to the qualifications, functions, or duties of the business or profession for which the license was issued, or the ground of knowingly making a false statement of fact required to be revealed in an application for such license. A conviction within the meaning of this section means a plea or verdict of guilty or a conviction following a plea of nolo contendere. Any action which a board is permitted to take following the establishment of a conviction may be taken when the time for appeal has elapsed, or the judgment of conviction has been affirmed on appeal, or when an order granting probation is made suspending the imposition of sentence, irrespective of a subse-

quent order under the provisions of Section 1203.4 of the Penal Code."

10. Business and Professions Code section 2261 provides that, "Knowingly making or signing any certificate or other document directly or indirectly related to the practice of medicine or podiatry which falsely represents the existence or nonexistence of a state of facts, constitutes unprofessional conduct."

11. Business and Professions Code section 2262 states that:

"Altering or modifying the medical record of any person, with fraudulent intent, or **creating any false medical record, with fraudulent intent**, constitutes unprofessional conduct.

"In addition to any other disciplinary action, the Division of Medical Quality or the California Board of Podiatric Medicine may impose a civil penalty of five hundred dollars ($500) for a violation of this section." [Emphasis added.]

FIRST CAUSE FOR DISCIPLINE

(Conviction of Substantially Related Crime)

12. Respondent is subject to disciplinary action for engaging in unprofessional conduct under Business and Professions Code section 2236, 490, because he was convicted of a crime substantially related to the qualifications, functions, or duties of a physician and surgeon. The relevant facts and circumstances are as follows.

Criminal Case

13. On or about September 26, 1997, an Information was filed against respondent in the matter entitled "United States of America v. Robert A. Fiddes," before the United States District Court for the Central District of California, Case No. CR-97-927. Said Information charged respondent with violating 18 U.S.C., sections 371, 1001 ("Conspiracy to Commit the Crime of Knowingly and Willingly Making False Statements regarding a Material Matter Within the Jurisdiction of the U.S. Food and Drug Administration").

14. On or about September 26, 1997, respondent executed a plea agreement with the United States Attorney's Office in which respondent waived indictment by grand jury and pled guilty to the one-count Information described in the preceding paragraph.

15. On or about September 30, 1997, the Court in this matter questioned respondent regarding the plea of guilty and found it knowledgeable and voluntary, and ordered the plea accepted and entered.

16. The circumstances of the crime committed by respondent were acknowledged to be true in the plea agreement entered into by respondent with the concurrence of his counsel, and include the facts listed below.

Underlying Facts

17. From about 1992 through 1997, respondent was the owner and president of American Pharmaceutical Research, Inc.,

formerly known as Southern California Research, Inc. (collectively known as "SCRI").

18. SCRI was a private company which contracted with drug manufacturers to conduct clinical studies of new pharmaceutical products in connection with the FDA drug approval process. Respondent was the principal investigator for all drug research at SCRI.

19. Beginning on a date unknown and continuing at least through December 1, 1996, respondent and two other individuals conspired to make false statements to drug manufacturers and, thereby, to the FDA, in order to enable SCRI to receive substantial payments from drug manufacturers. Such payments, totalling at least $870,000.00, were received for conducting drug studies in which false and fraudulent information was knowingly provided, thereby resulting in the manufacturers' submission of false pre-marketing evaluations to the FDA that were used in determining the safety and efficacy of the particular drug being studied.

20. False and fraudulent acts of respondent included, but were not limited to:

(1) In or around May of 1995, in connection with a drug study sponsored by Pharmaco-Organon involving a drug product known as Triphasic Pill, with respondent's knowledge and approval, personal data relating to individuals with the initials L.C. and D.H. or their family members was used in creating documentation falsely indicating that individuals with the initials V.H. and L.M.C. were fully participating in the study,

when in fact these two individuals were not participating.

(2) In or around April of 1996, in connection with a drug study coordinated by respondent and sponsored by SmithKline Beecham involving a drug product known as Eprosartan 090, respondent was aware that the study protocol required that enrollees possess a certain proteinuria level in their urine. Because it was difficult to enroll patients with the required proteinuria levels, at respondent's direction, an individual whose initials are D.J., along with other study coordinators, substituted urine with the required proteinuria level for the urine of otherwise non-qualifying patients so that those patients could be enrolled in the study.

(3) In or around the summer of 1996, in connection with a drug study sponsored by PPD/Zambon involving a drug product known as PHZ-136, respondent concealed the enrollment of non-qualifying patients in the study by directing an individual with the initials L.C. to cause the destruction of x-ray film reports showing that those patients did not have osteoarthritis of the knee as required by the study protocol.

(4) In or about March of 1996, in connection with a drug study coordinated by respondent and sponsored by Bayer involving a drug product known as Clotrimazole, respondent, along with L.C. and D.H., enrolled "fake" patients in the study. In particular, respondent and those two individuals assisted one another in falsifying study documentation to make it appear as if more than 25 patients participated in the study when in fact only one participated.

21. Respondent has been convicted of a crime substantially related to the qualifications, functions, or duties of a physician and surgeon, in that the crime for which respondent has been convicted was committed in the course of his medical research practice, with reference to individuals whom he falsely represented to be test subjects of that medical research practice, and with reference to false statements of test data and unsupported medical conclusions made in connection with that medical research practice.

SECOND CAUSE FOR DISCIPLINE

(Dishonest or Corrupt Acts)

22. Respondent is subject to disciplinary action for unprofessional conduct under Business and Professions Code section 2234, subdivision (e), because he engaged in dishonest or corrupt acts substantially related to the practice of medicine. The relevant facts and circumstances ensue.

23. Complainant realleges Paragraphs 12 though 21, inclusive, as if set forth in full hereat.

24. Respondent submitted bills for the false "medical research" he performed, and did not disclose on said bills that his data was falsified or that he had done anything other than perform the services his client had requested.

25. The submission of false data by respondent was substantially related to the qualifications, functions, or duties of a physician and surgeon because it was committed in the course and scope of his medical research practice, which used his skills

and training as a physician. The falsification of data was involved either "patients" or "test subjects" of his medical research practice. Respondent used his skills, knowledge, and training to enunciate unsupported medical conclusions and to issue data which he knew would be relied upon by drug manufacturers (which need to assess their legal liability, protect professional reputations and public perceptions, consider stockholders' interests, and promote only efficacious drugs) and the FDA (which is charged with protecting the public). By submitting fictitious medical documentation of research data, respondent placed at serious health risk a patient population which would rely upon the safety and efficacy of the new drugs being evaluated.

THIRD CAUSE FOR DISCIPLINE

(Making False Documents)

26. Respondent is subject to disciplinary action for unprofessional conduct under Business and Professions Code section 2261, because he knowingly made documents directly or indirectly related to the practice of medicine which falsely represents the existence or nonexistence of a state of facts. The relevant facts and circumstances ensue.

27. Complainant realleges Paragraphs 12 though 25, inclusive, as if set forth in full hereat.

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FOURTH CAUSE FOR DISCIPLINE

(Altering Medical Records/ Creating False Medical Records)

28. Respondent is subject to disciplinary action for unprofessional conduct under Business and Professions Code section 2262, because he altered or modified medical records with fraudulent intent, and/or created any false medical record with fraudulent intent. The relevant facts and circumstances ensue.

29. Complainant realleges Paragraphs 12 though 27, inclusive, as if set forth in full hereat.

OTHER MATTERS

30. Business and Professions Code section 125.3 provides in pertinent part that:

> "(a) Except as provided by law, in any order issued in resolution of a disciplinary proceeding before any board within the department ... the board may request the administrative law judge to direct a licentiate found to have committed a violation or violations of the licensing act to pay a sum not to exceed the reasonable costs of the investigation and enforcement of the case. ...
>
> "(c) A certified copy of the actual costs, or a good faith estimate of costs where actual costs are not available, signed by the entity bringing the proceeding or its designated representative shall be prima facie evidence of reasonable costs of investigation and prosecution of the case. The costs shall include the amount of investigative and enforcement costs up to the date of the hearing, inclu-

ding, but not limited to, charges imposed by the Attorney General.

"(d) The administrative law judge shall make a proposed finding of the amount of reasonable costs of investigation and prosecution of the case when requested pursuant to subdivision (a). The finding of the administrative law judge with regard to costs shall not be reviewable by the board to increase the cost award. The board may reduce or eliminate the cost award, or remand to the administrative law judge where the proposed decision fails to make a finding on costs requested pursuant to subdivision (a)...."

31. Section 16.01 of the 1997/1998 Budget Act of the State of California provides, in pertinent part, that:

"(a) No funds appropriated by this act may be expended to pay any Medi-Cal claim for any service performed by a physician while that physician's license is under suspension or revocation due to disciplinary action of the Medical Board of California.

"(b) No funds appropriated by this act may be expended to pay any Medi-Cal claim for any surgical services or other invasive procedure performed on any Medi-Cal beneficiary by a physician if that physician has been placed on probation due to a disciplinary action of the Medical Board of California related to the performance of that specific service or procedure on any patient, except in any case where the board makes a determination during its disciplinary process that there exist compelling

circumstances that warrant continued Medi-Cal reimbursement during the probationary period."

PRAYER

32. For the reasons set forth in paragraphs 1 through 31, inclusive, of this accusation, good cause exists to impose discipline upon the Physician's and Surgeon's Certificate issued to respondent.

WHEREFORE, complainant requests that a hearing be held on the matters herein alleged, and that following the hearing, the Division issue a decision:

1. Revoking or suspending Physician's and Surgeon's Certificate No. A24377, heretofore issued to respondent Robert Alan Fiddes, M.D.;

2. Revoking, suspending or denying approval of the respondent's authority to supervise physician's assistants, pursuant to Business and Professions Code section 3527;

3. Imposing upon respondent a civil penalty of five hundred dollars ($500) for each act of unprofessional conduct as defined in Business and Professions Code section 2262;

4. Ordering respondent to pay the Board the actual and reasonable costs of the investigation and enforcement of this case, and, if placed on probation, ordering respondent to pay the costs of probation monitoring; and

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4. Taking such other and further action as the Division deems necessary and proper.

DATED: June 26, 1998.

Ron Joseph
Executive Director
Medical Board of California
Department of Consumer Affairs
State of California

Complainant

BEFORE THE
DIVISION OF MEDICAL QUALITY
MEDICAL BOARD OF CALIFORNIA
DEPARTMENT OF CONSUMER AFFAIRS
STATE OF CALIFORNIA

In the Matter of the Accusation Against:	)	
	)	No. 11-97-79246
ROBERT ALAN FIDDES, M.D. Certificate No. A-24377	)	**STATEMENT TO RESPONDENT**
Respondent	)	

RESPONDENT ABOVE - NAMED:

There is attached hereto a copy of an Accusation which has been filed with the office of the State agency named herein and which is hereby served upon you.

Unless a written request for a hearing signed by you or on your behalf is delivered or mailed to the agency named herein within fifteen (15) days after a copy of the Accusation was personally served on you or mailed to you, you will be deemed to have waived your right to a hearing in this matter and the agency may proceed upon the Accusation without a hearing and may take action thereon as provided by law.

The request for a hearing may be made by delivering or mailing one of the enclosed forms entitled "Notice of Defense" or by delivering or mailing a notice of Defense as provided in Section 11506 of the Government Code to the Deputy Attorney General in this case, whose name, address and telephone number appear on the front page of the Accusation.

The hearing may be postponed for a good cause. If you have good cause, you are obliged to notify the agency or, if an administrative law judge has been assigned to the hearing, the Office of Administrative Hearings, within 10 working days after you discover the good cause. Failure to notify the agency within 10 days will deprive you of a postponement.

You may, but need not, be represented by counsel at any or all stages of these proceedings. The enclosed Notice of Defense, if signed and filed with the above - designated agency shall be deemed a specific denial of all parts of the Accusation, but you will not be permitted to raise any objection to the form of the Accusation unless you file a further Notice of Defense as provided in Section 11506 of the Government Code within fifteen (15) Days after service of the Accusation upon you.

If you file any Notice of Defense within the time permitted, a hearing will be had upon the charges made in the Accusation.

Copies of Section 11507.5, 11507.6 and 11507.7 of the Government Code are attached.

If you desire the names and addresses of witnesses or an opportunity to inspect and copy the items mentioned in Section 11507.6 of the Government Code in the possession, custody or control of the agency, you may contact the Deputy Attorney General, whose name, address, and telephone number appear on the first page of the Accusation.

STIPULATED SETTLEMENTS

Very often, administrative cases are settled by the parties through discussions and negotiations. Our procedures do not include a formal settlement conference, which is a common procedure in civil court cases. However, all parties in this case should get together at the earliest time to discuss any possible stipulations or settlement that can be mutually agreed upon.

All Stipulated settlement of cases are subject to the approval of the Division of Medical Quality. The Division has published a booklet (a copy is enclosed) setting forth its disciplinary guidelines and model disciplinary orders. By looking up your relevant code violations in this booklet, you can learn the penalty ranges and conditions acceptable to the Division.

COPY OF GOVERNMENT CODE SECTIONS 11507.5, 11507.6 AND 11507.7

PROVIDED PURSUANT TO GOVERNMENT CODE SECTIONS 11504 AND 11505

SECTION 11507.5: DISCOVERY LIMITATIONS

The provisions of Section 11507.6 provide the exclusive right to and method of discovery as to any proceeding governed by this chapter.

SECTION 11507.6: Discovery Rights & Procedures

After initiation of a proceeding in which a respondent or other party is entitled to a hearing on the merits, a party, upon written request made to another party, prior to the hearing and within 30 days after service by the agency of the initial pleading or within 15 days after the service of an additional pleading, is entitled to (1) obtain the names and addresses of witnesses to the extent known to the other party, including, but not limited to, those intended to be called to testify at the hearing, and (2) inspect and make a copy of any of the following in the possession or custody or under the control of the other party:

(a) A statement of a person, other than the respondent, named in the initial administrative pleading, or in any additional pleading, when it is claimed that the act or omission of the respondent as to this person is the basis for the administrative proceeding;

(b) A statement pertaining to the subject matter of the proceeding made by any party to another party or person;

(c) Statements of witnesses then proposed to be called by the party and of other persons having personal knowledge of the acts, omissions or events which are the basis for the proceeding, not included in (a) or (b) above;

(d) All writings, including, but not limited to, reports of mental, physical and blood examinations and things which the party then proposes to offer in evidence;

(e) Any other writing or thing which is relevant and which would be admissible in evidence;

(f) Investigative reports made by or on behalf of the agency or other party pertaining to the subject matter of the proceeding, to the extent that these reports (1) contain the names and addresses of witnesses or of persons having personal knowledge of the acts, omissions or events which are the basis for the proceeding, or (2) reflect matters perceived by the investigator in the course of his or her investigation, or (3) contain or include by attachment any statement or writing described in (a) to (e),inclusive, or summary thereof.

For the purpose of this section, "statements" include written statements by the person signed or otherwise authenticated by him or her, stenographic, mechanical, electrical or other recordings, or transcripts thereof, of oral statements by the person, and written reports or summaries of these oral statements.

Nothing in this section shall authorize the inspection or copying of any writing or thing which is privileged from disclosure by law or otherwise made confidential or protected as the attorney's work product.

(g) In any proceeding under subdivision (i) or (j) of Section 12940, or Section 19572 or 19702, alleging conduct which constitutes sexual harassment, sexual assault, or sexual battery, evidence of specific instances of a complainant's sexual conduct with individuals other than the alleged perpetrator is not discoverable unless it is to be offered at a hearing to attack the credibility of the complainant as provided for under subdivision (j) of Section 11513. This subdivision is intended only to limit the scope of discovery; it is not intended to affect the methods of discovery allowed under this section.

SECTION 11507.7: Petition to compel discovery; Order; Sanctions

(a) Any party claiming the party's request for discovery pursuant to Section 11507.6 has not been complied with may serve and file with the administrative law judge a motion to compel discovery, naming as respondent the party refusing or failing to comply with Section 11507.6. The motion shall state facts showing the respondent party failed or refused to comply with Section 11507.6, a description of the matters sought to be discovered, the reason or reasons why the matter is discoverable under that section, that a reasonable and good faith attempt to contact the respondent for an informal resolution of the issue has been made, and the ground or grounds of respondent's refusal so far as known to the moving party.

(b) The motion shall be served upon respondent party and filed within 15 days after the respondent party first evidenced failure or refusal to comply with Section 11507.6 or within 30 days after request was made and the party has failed to reply to the request, or within another time provided by stipulation, whichever period is longer.

(c) The hearing on the motion to compel discovery shall be held within 15 days after the motion is made, or a later time that the administrative law judge may on the judge's own motion for good cause determine. The respondent party shall have the right to serve and file a written answer or other response to the motion before or at the time of the hearing.

(d) Where the matter sought to be discovered is under the custody or control of the respondent party and the respondent party asserts that the matter is not a discoverable matter under the provisions of Section 11507.6, or is privileged against disclosure under those provisions, the administrative law judge may order lodged with it matters provided in subdivision (b) of Section 915 of the Evidence Code and examine the matters in accordance with it provisions.

(e) The administrative law judge shall decide the case on the matters examined in camera, the papers filed by the parties, and such oral argument and additional evidence as the administrative law judge may allow.

(f) Unless otherwise stipulated by the parties, the administrative law judge shall no later than 15 days after the hearing make it order denying or granting the motion. The order shall be in writing setting forth the matters the moving party is entitled to discover under Section 11507.6. A copy of the order shall forthwith be served by mail by the administrative law judge upon the parties. Where the order grants the motion in whole or part, the order shall not become effective until 10 days after the date the order is served. Where the order denies relief to the moving party, the order shall be effective on the date it is served.

****

DECLARATION OF SERVICE BY UNITED STATES CERTIFIED MAIL

In the Matter of the Accusation Against:

ROBERT ALAN FIDDES, M.D. 11-97-79246

I, the undersigned, declare that I am over 18 years of age and not a party to the within cause; my business address is 1430 Howe Avenue, Sacramento, California 95825. I served a true copy of the attached:

STATEMENT TO RESPONDENT; ACCUSATION; REQUEST FOR DISCOVERY; GOVERNMENT CODE SECTIONS 11507.5, 11507.6, 11507.7; NOTICE OF DEFENSE FORM (2 COPIES); NOTIFICATION REGARDING STATE BUDGET ACT SECTION 16.01; A MANUAL OF DISCIPLINARY GUIDELINES AND MODEL DISCIPLINARY ORDERS

by U.S. Certified mail on each of the following, by placing same in an envelope (or envelopes) addressed (respectively) as follows:

NAME AND ADDRESS	CERTIFICATION #
Robert A. Fiddes, M.D. 12291 E. Washington Boulevard, No. 106 Whittier, CA 90606	P 115 268 926

Elisa B. Wolfe
Deputy Attorney General
Department of Justice
300 South Spring Street, Suite 5212
Los Angeles, CA 90013-1233

Each said envelope was then, on **June 26, 1998**, sealed and deposited in the United States mail at Sacramento, California, the county in which I am employed, with the postage thereon fully prepaid.

Executed on **June 26, 1998** at Sacramento, California.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Declarant

DECLARATION OF SERVICE BY CERTIFIED MAIL

In the Matter of the Accusation:

Re: Against: ROBERT A. FIDDES, M.D. No: 11-97-79246

I, the undersigned, declare that I am over 18 years of age and not a party to the within cause; my business address is 1430 Howe Avenue, Sacramento, California 95825. I served a true copy of the attached:

STATEMENT TO RESPONDENT; ACCUSATION; REQUEST FOR DISCOVERY; GOVERNMENT CODE SECTIONS 11507.5, 11507.6, 11507.7; NOTICE OF DEFENSE FORM (2 COPIES); NOTIFICATION REGARDING STATE BUDGET ACT SECTION 16.01; A MANUAL OF DISCIPLINARY GUIDELINES AND MODEL DISCIPLINARY ORDERS

by certified mail on each of the following, by placing same in an envelope (or envelopes) addressed (respectively) as follows:

NAME AND ADDRESS	CERTIFIED
Robert A. Fiddes, M.D. 1413 Via Davalos Palos Verdes Estates, CA 90274	Z 249 229 897

Elisa B. Wolfe
Deputy Attorney General
Office of the Attorney General
300 South Spring Street, Suite 5212
Los Angeles, CA 90013-1233

Each said envelope was then, on August 17, 1998, sealed and deposited in the United States mail at Sacramento, California, the county in which I am employed, as certified mail, with the postage thereon fully prepaid, and return receipt requested.

Executed on August 17, 1998, at Sacramento, California. I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

DECLARANT

DECLARATION OF SERVICE BY U.S. MAIL

In the Matter of the Accusation against:

Re: ROBERT ALAN FIDDES, M.D. No: 11-97-79246

I, the undersigned, declare that I am over 18 years of age and not a party to the within cause; my business address is 1430 Howe Avenue, Sacramento, California 95825. I served a true copy of the attached:

STATEMENT TO RESPONDENT; ACCUSATION; REQUEST FOR DISCOVERY; GOVERNMENT CODE SECTIONS 11507.5, 11507.6, 11507.7; NOTICE OF DEFENSE FORM (2 COPIES); NOTIFICATION REGARDING STATE BUDGET ACT SECTION 16.01; A MANUAL OF DISCIPLINARY GUIDELINES BOOKLET AND MODEL DISCIPLINARY ORDERS

by U.S. Mail on each of the following, by placing same in an envelope (or envelopes) addressed (respectively) as follows:

NAME AND ADDRESS

Robert A. Fiddes, M.D. — Address of Record
12291 E. Washington Boulevard, No. 106
Whittier, CA 90606

Robert A. Fiddes, M.D.
1413 Via Davalos
Palos Verdes Estates, CA 90274-1943

Elisa B. Wolfe
Deputy Attorney General
Department of Justice
300 South Spring Street, Suite 5212
Los Angeles, CA 90013-1233

Each said envelope as then, on October 8, 1998, sealed and deposited in the United States mail at Sacramento, California, the county in which I am employee with the postage thereon fully prepaid.

Executed on October 8, 1998, at Sacramento, California. I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Arlene Kayenda
DECLARANT

DECLARATION OF SERVICE BY UNITED STATES MAIL

In the Matter of the Accusation Against:

ROBERT ALAN FIDDES, M.D. **11-97-79246**

I, the undersigned, declare that I am over 18 years of age and not a party to the within cause; my business address is 1430 Howe Avenue, Sacramento, California 95825. I served a true copy of the attached:

STATEMENT TO RESPONDENT; ACCUSATION; REQUEST FOR DISCOVERY; GOVERNMENT CODE SECTIONS 11507.5, 11507.6, 11507.7; NOTICE OF DEFENSE FORM (2 COPIES); NOTIFICATION REGARDING STATE BUDGET ACT SECTION 16.01; A MANUAL OF DISCIPLINARY GUIDELINES AND MODEL DISCIPLINARY ORDERS

by U.S. First Class mail on each of the following, by placing same in an envelope (or envelopes) addressed (respectively) as follows:

NAME AND ADDRESS **CERTIFICATION #**

Brian Sun, Esq.
100 Wilshire Boulevard, Suite 700
Santa Monica, CA 90401

Elisa B. Wolfe
Deputy Attorney General
Department of Justice
300 South Sprig Street, Suite 5212
Los Angeles, CA 90013-1233

Each said envelope was then, on **October 22, 1998**, sealed and deposited in the United States mail at Sacramento, California, the county in which I am employed, with the postage thereon fully prepaid.

Executed on **October 22, 1998** at Sacramento, California.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Declarant

DECLARATION OF SERVICE BY UNITED STATES CERTIFIED MAIL

In the Matter of the Accusation Against:

ROBERT A. FIDDES, M.D. **11-97-79246**

I, the undersigned, declare that I am over 18 years of age and not a party to the within cause; my business address is 1430 Howe Avenue, Sacramento, California 95825. I served a true copy of the attached:

STATEMENT TO RESPONDENT; ACCUSATION; REQUEST FOR DISCOVERY; GOVERNMENT CODE SECTIONS 11507.5, 11507.6, 11507.7; NOTICE OF DEFENSE FORM (2 COPIES); NOTIFICATION REGARDING STATE BUDGET ACT SECTION 16.01; DECLARATION OF SERVICE BY U.S. MAIL DATED OCTOBER 22, 1998 (to Brian Sun, Esq.); A MANUAL OF DISCIPLINARY GUIDELINES AND MODEL DISCIPLINARY ORDERS

by U.S. Certified mail on each of the following, by placing same in an envelope (or envelopes) addressed (respectively) as follows:

NAME AND ADDRESS	**CERTIFICATION #**
Robert A. Fiddes # 12574-112 L.A. Metropilitan Detention Center 535 No. Alameda Street Los Angeles, CA 90012	Z 249 229 991

Elisa B. Wolfe
Deputy Attorney General
Department of Justice
300 South Spring Street
Los Angeles, CA 90013-1233

Each said envelope was then, on **November 25, 1998**, sealed and deposited in the United States mail at Sacramento, California, the county in which I am employed, with the postage thereon fully prepaid.

Executed on **November 25, 1998** at Sacramento, California.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Declarant

11-97-79246 (ACC)

SENDER:
- Complete items 1 and/or 2 for additional services.
- Complete items 3, 4a, and 4b.
- Print your name and address on the reverse of this form so that we can return this card to you.
- Attach this form to the front of the mailpiece, or on the back if space does not permit.
- Write *"Return Receipt Requested"* on the mailpiece below the article number.
- The Return Receipt will show to whom the article was delivered and the date delivered.

I also wish to receive the following services (for an extra fee):
1. ☐ Addressee's Address
2. ☐ Restricted Delivery

Consult postmaster for fee.

3. Article Addressed to:

Robert Alan Fiddes, M.D.
#12574-112
L.A. Metro Detention Center
535 No. Alameda Street
Los Angeles, CA 90012

4a. Article Number
Z 249 229 991

4b. Service Type
☐ Registered ☒ Certified
☐ Express Mail ☐ Insured
☐ Return Receipt for Merchandise ☐ COD

7. Date of Delivery
11-30-98

5. Received By: *(Print Name)*

8. Addressee's Address *(Only if requested and fee is paid)*

6. Signature: *(Addressee or Agent)*
X

PS Form 3811, December 1994 102595-98-B-0229 Domestic Return Receipt

Is your RETURN ADDRESS completed on the reverse side?

Thank you for using Return Receipt Service.

UNITED STATES POSTAL SERVICE

First-Class Mail
Postage & Fees Paid
USPS
Permit No. G-10

● Print your name, address, and ZIP Code in this box ●.

MEDICAL BOARD OF CALIFORNIA
1426 Howe Avenue, Suite 54
Sacramento, CA 95825-3236
Attn: Arlene Krysinski

RECEIVED
DEC - 4 1998
MEDICAL BOARD OF CALIFORNIA
CENTRAL FILE ROOM

EXHIBIT "2"

11-97-79246 (ACC)

SENDER:
- Complete items 1 and/or 2 for additional services.
- Complete items 3, 4a, and 4b.
- Print your name and address on the reverse of this form so that we can return this card to you.
- Attach this form to the front of the mailpiece, or on the back if space does not permit.
- Write "*Return Receipt Requested*" on the mailpiece below the article number.
- The Return Receipt will show to whom the article was delivered and the date delivered.

I also wish to receive the following services (for an extra fee):
1. ☐ Addressee's Address
2. ☐ Restricted Delivery

Consult postmaster for fee.

3. Article Addressed to:

Robert A. Fiddes, M.D.
12291 E. Washington Blvd., No. 106
Whittier, CA 90606

4a. Article Number
P 115 268 926

4b. Service Type
☐ Registered ☒ Certified
☐ Express Mail ☐ Insured
☐ Return Receipt for Merchandise ☐ COD

7. Date of Delivery

5. Received By: *(Print Name)*

8. Addressee's Address *(Only if requested and fee is paid)*

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VIA DA LOS

Robert A. Fiddes, M.D.
12291 E. Washington Boulevard, No. 106
Whittier, CA 90606

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1413 Via Davalos
Palos Verdes Estates, CA 90274

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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9544 '02 MAY -8 P1:34

Elaine Yee-Ling Lai
17200 Monaco Drive
Cerritos, CA 90703

PROPOSAL TO DEBAR
NOTICE OF OPPORTUNITY FOR HEARING
Docket No. 00N-1529

Dear Ms. Lai:

This letter is to inform you that the Food and Drug Administration (FDA) is proposing to issue an order debarring you for a period of 5 years from providing services in any capacity to a person that has an approved or pending drug product application. The FDA bases this proposal on a finding that you were convicted of a felony for aiding and abetting the making of a false document containing a materially fictitious statement in a matter within the jurisdiction of a government agency, and that your conduct undermined the process for the regulation of drugs. This letter also offers you an opportunity for a hearing on the proposal.

Conduct Related to Debarment

On June 9, 1998, the United States District Court for the Central District of California accepted your plea of guilty to one count of aiding and abetting the making of a false document containing a materially fictitious statement in a matter within the jurisdiction of a government agency, in violation of 18 U.S.C. sections 1001(a)(3) and 2. The underlying facts supporting this felony conviction are as follows:

You were employed by American Pharmaceutical Research, Inc., formerly known as Southern California Research Institute (collectively SCRI), as the Chief Operating Officer from about March 1996 through March 1997. SCRI was a private company retained by drug manufacturers to conduct clinical studies of new pharmaceutical products to be submitted to FDA in support of approval of the drug products. Dr. Robert A. Fiddes was the owner and president of SCRI and the principal investigator for all drug research conducted at SCRI.

In April 1996, SCRI was hired to conduct a study on a drug product known as Eprosartan 090. The study protocol for this drug required that subjects possess a certain level of proteinuria in their urine to be eligible to participate in the study. Because it was difficult to enroll subjects with the required proteinuria levels, Dr. Fiddes paid an SCRI study coordinator whose urine had

the required proteinuria levels for the use of her urine. Dr. Fiddes substituted the urine of the study coordinator for the urine of otherwise ineligible subjects so that those subjects could be enrolled in the study. You were aware that Dr. Fiddes was paying the study coordinator for the use of her urine and of the improper urine substitution.

From about June 1996 to August 1996, you knowingly and willfully assisted Dr. Fiddes in making a fraudulent document that contained false and fictitious material statements and entries. Specifically, to conceal the urine substitution from the FDA, you assisted Dr. Fiddes in creating a false subject chart for the study coordinator to make it appear that she was a subject of Dr. Fiddes and was submitting her urine in connection with treatment by Dr. Fiddes. You assisted in creating the fraudulent document with the intent to influence FDA's decision about the Eprosartan 090 drug study.

FDA's Finding

Section 306(b)(2)(B)(i)(II) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(b)(2)(B)(i)(II)) permits the FDA to debar an individual if it finds that the individual has been convicted of a felony under Federal law for conspiracy to commit, or aiding or abetting a criminal offense relating to the development or approval, including the process for the development or approval, of any drug product, or otherwise relating to the regulation of drug products under the Act and that the offense undermines the process for the regulation of drugs. Your felony conviction under 18 U.S.C. sections 1001(a)(3) and 2 was for aiding and abetting in making fraudulent documents and statements for use by FDA to determine whether a new drug should be approved, an offense related to the development or approval of any drug product. Accordingly, the Agency finds that you are eligible for permissive debarment.

Under section 306(l)(2) of the Act, permissive debarment may be applied when an individual is convicted within the 5 years preceding this notice. You were convicted on June 9, 1998, less than 5 years ago. The Agency may debar you for up to 5 years for each offense, and can determine whether the debarment period for multiple offenses shall run concurrently or consecutively (306(c)(2)(A) of the Act) (21 U.S.C. 335a(c)(2)(A)).

Section 306(c)(3) of the Act provides six factors for consideration in determining the appropriateness of and the period of permissive debarment for a person (21 U.S.C. 335a(c)(3)). These are as follows:

(A) the nature and seriousness of any offense involved,

(B) the nature and extent of management participation in any offense involved, whether corporate policies and practices encouraged the offense, including whether inadequate institutional controls contributed to the offense,

(C) the nature and extent of voluntary steps to mitigate the impact on the public of any offense involved, including the recall or the discontinuation of the distribution of suspect drugs, full cooperation with any investigations (including the extent of disclosure to appropriate authorities of all wrongdoing), the relinquishing of profits on drug approvals fraudulently obtained, and any other actions taken to substantially limit potential or actual adverse effects on the public health,

(D) whether the extent to which changes in ownership, management, or operations have corrected the causes of any offense involved and provide reasonable assurances that the offense will not occur in the future,

(E) whether the person to be debarred is able to present adequate evidence that current production of drugs subject to abbreviated drug applications and all pending abbreviated drug applications are free of fraud or material false statements, and

(F) prior convictions under this Act or under other Acts involving matters within the jurisdiction of the Food and Drug Administration.

The Agency considers that four of these factors are applicable for consideration:

1. The nature and seriousness of the offense involved (Factor A)

You were convicted of one count of aiding and abetting the making of a materially false document based on your assistance in fabricating a subject chart to conceal study protocol violations involving the drug Eprosartan 090, which was being studied for the treatment of diabetes and hypertension.

The Agency finds that your conduct undermined the integrity of the drug approval or regulatory process. You knowingly assisted in creating fraudulent study data to be used by FDA in determining whether to approve Eprosartan 090. Your illegal conduct was intended to affect FDA's regulatory decision about the drug. Accordingly, the Agency will consider the nature and seriousness of your conduct an unfavorable factor.

Further, diabetes and hypertension are serious and potentially life-threatening diseases. Accordingly, the Agency will consider your conduct an extremely unfavorable factor because your actions potentially undermined the safety or effectiveness of a drug used for a serious or life-threatening condition.

2. The nature and extent of management participation in any offense involved whether corporate policies and practices encouraged the offense, including whether inadequate institutional controls contributed to the offense (Factor B)

You participated in the planning of the conduct underlying the conviction. You knew of the improper urine substitutions and helped Dr. Fiddes to falsify records to conceal the misrepresentations from the FDA. Accordingly, the Agency considers the nature and extent of your participation an unfavorable factor.

3. The nature and extent of voluntary steps to mitigate the impact on the public of any offense involved, including the recall or the discontinuation of the distribution of suspect drugs, full cooperation with any investigations (including the extent of disclosure to appropriate authorities of all wrongdoing), the relinquishing of profits on drug approvals fraudulently obtained, and any other actions taken to substantially limit potential or actual adverse effects on the public health (Factor C)

You did not disclose to appropriate authorities all wrongdoing, and in fact took affirmative actions to conceal wrongdoing. Further, you did not report drug related violations nor did you take action to correct violations although you knew that the actions were violative of the law. Therefore, the Agency will consider the nature and extent of mitigation as an unfavorable factor.

4. Prior convictions under this Act or under other Acts involving matters within the jurisdiction of the Food and Drug Administration (Factor F)

The Agency is unaware of any prior convictions.

Proposed Action and Notice of Opportunity for Hearing

Based on the findings discussed above, the FDA proposes to issue an order under section 306(b)(2) of the Act, debarring you from providing services in any capacity to a person that has an approved or pending drug product application for one period of 5 years. You were convicted of one count of aiding and abetting the making of a false document containing a materially fictitious statement in a matter within the jurisdiction of a government agency, a felony described in section 306(b)(2)(B)(i) and (a)(2). Since you were convicted of one count, FDA finds you committed one offense. The Agency intends to implement the maximum debarment period for the offense, based on the factors discussed above.

Elaine Yee-Ling Lai

In accordance with section 306 of the Act and 21 CFR part 12, you are hereby given an opportunity for a hearing to show why you should not be debarred as proposed in this letter. If you decide to seek a hearing, you must file: (1) on or before 30 days from the date of receipt of this letter, a written notice of appearance and request for hearing, and (2) on or before 60 days from the date of receipt of this letter, the information on which you rely to justify a hearing. The procedures and requirements governing this notice of opportunity for a hearing, notice of appearance and request for a hearing, information and analyses to justify a hearing, and determination of a grant or denial of a hearing are contained in 21 CFR part 12 and section 306(i) of the Act (21 U.S.C. 335a(i)).

Your failure to file a timely written notice of appearance and request for hearing constitutes an election by you not to use the opportunity for a hearing on your debarment, and a waiver of any contentions concerning this action. If you do not request a hearing in the manner prescribed by the regulations, the Agency will not hold a hearing and will issue the debarment order as proposed in this letter.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the information and factual analyses in your request for a hearing that there is no genuine and substantial issue of fact that precludes the order of debarment, the Commissioner of Food and Drugs will enter summary judgment against you, making findings and conclusions, and denying a hearing.

You should understand that the facts underlying your conviction are not at issue in this proceeding. The only material issue is whether you were convicted as alleged in this notice and, if so, whether, as a matter of law, this conviction permits your debarment as proposed.

Your request for a hearing, including any information or factual analyses relied on to justify a hearing, must be identified with Docket No. 00N-1529 and sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. You must file four copies of all submissions under this notice of opportunity for hearing. The public availability of information in these submissions is governed by 21 CFR 10.20(j). Publicly available submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Elaine Yee-Ling Lai

This notice is issued under the Federal Food, Drug, and Cosmetic Act (section 306 (21 U.S.C. 335a)) and under authority delegated to the Director of the Center for Drug Evaluation and Research (21 CFR 5.99).

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

A Doctor's Drug Trials Turn Into Fraud

By KURT EICHENWALD and GINA KOLATA
Published: May 17, 1999

Editor's Note Appended

If ever there was a wonder boy in the lucrative business of drug testing, it was Dr. Robert Fiddes.

In just a few years, Dr. Fiddes transformed his sleepy medical practice here into a research juggernaut, recruiting patients for drug experiments at a breakneck pace. His success made him a magnet for an industry desperately scouring the nation for test subjects. Companies large and small showered him not only with more than 170 studies to conduct, but with millions of dollars in compensation for his work.

Life was good. With bank accounts bulging, Dr. Fiddes and his wife could afford to drive matching BMW's; a Ferrari parked in his garage was ready for special occasions. After a short time in research, the once small-time family practitioner was planning his dream house on a Cayman Islands beach and envisioning the day he would make millions more by selling shares in his business to the public.

But amid the glitter and cash was a fact that no one outside his office knew: It was all a scam.

For Dr. Fiddes was conducting research fraud of audacious proportions, cutting corners and inventing data to keep the money flowing from the drug industry. Fictitious patients were enrolled in studies. Blood pressure readings were fabricated. Bodily fluids that met certain lab values were kept on hand in the office refrigerator, ready to be substituted for the urine or blood of patients who did not qualify for studies.

Monitors for the Government and the industry never noticed any problems with Dr. Fiddes's bogus paperwork, which they reviewed during routine audits. Even when some of Dr. Fiddes's employees alerted those monitors to their suspicions, no investigations were initiated. Instead, their warnings were filed away, while Dr. Fiddes's sterling reputation as a researcher grew.

Finally, in June 1996, the scheme started to unravel when the manager of a neighboring doctor's office, Dennelle Del Valle, told a Government auditor rumors of crimes, lies and fraud she had heard from Dr. Fiddes's own employees. Eventually, to prove the claims, Ms. Del Valle slipped a piece of paper into the auditor's hand. On it was written a telephone number and a single name: Susan. It was the tip that would lead the Government to Susan Lester, a former employee of Dr. Fiddes who not only knew what had happened, but had a few records that seemed to back up her story.

So began the multiyear investigation of Dr. Fiddes's Southern California Research Institute, a testing operation that was one of the most corrupt research enterprises ever discovered by law enforcement. The case is set to wind to a close this week, with the scheduled sentencing of the last co-conspirator. But in its wake is wreckage: Dr. Fiddes and several accomplices pleaded guilty to fraud, drug-study results for virtually every company in the business were compromised and the reliability of the private system for testing drugs for safety and efficacy has been thrown into question.

Dr. Fiddes "was putting the health of all these patients at risk," said Alan Knox, the former chief financial officer of Dr. Fiddes's research center, who resigned just months after taking the job when the investigation led him to learn of the fraud. "But he was also skewing samples that could affect the whole American public."

The abuses of this one doctor point to weaknesses in the new system developed in recent years for testing experimental drugs. No longer does the pharmaceutical industry rely on career researchers at academic medical centers, whose professional reputations are forged on the quality of their data. Rather, the industry has turned to thousands of private-practice doctors, for whom testing drugs has become a sideline for making money.

While the researchers and their incentives have changed, the methods of monitoring what they do remain basically the same even though now, since they are paid for each patient they recruit, researchers have an enormous financial incentive to cheat. The case of Dr. Fiddes underscores the ease with which such a system can be deceived -- a situation that has not been remedied since the discovery of his crimes.

The story of the corruption at the Southern California Research Institute was pieced together from memos and other internal documents, investigators' notes, drug company and court records, personal diaries and affidavits of participants, as well as interviews with Government officials, lawyers and the former employees and consultants at the company, which is now defunct.

The picture that emerges from these documents and interviews is of a research office ruled by a doctor driven by greed. Few employees other than the study coordinators -- mostly women of limited financial means -- were aware of the magnitude of the swindle. Those bothered by it were repeatedly assured that this was the way the drug industry worked. Faced with that perception, there seemed little they could do without risking their livelihood to stop the influential Dr. Fiddes, a man who believed that the system of monitoring was too poorly designed to ever

catch him.

"I don't think he thought he could be touched," said Kathryn Davis, a medical transcriber at the research center. "We just didn't understand why it had to go down the way it did. Maybe he just wanted too much too fast."

Through his lawyer, Dr. Fiddes -- who is now serving a 15-month sentence for fraud in the Metropolitan Detention Center in Los Angeles -- refused repeated requests for an interview. But in interviews with the Government after he agreed to plead guilty, Dr. Fiddes portrayed himself as a man trapped by the dishonesty of others. He maintained that most researchers are forced to cheat because drug companies issue requirements for test subjects that sound good in marketing material, but are impossible to meet in the real world. He said -- with no evidence to back up his claim -- that anyone successful in the business was skirting the rules.

Still, at his own research center, Dr. Fiddes laid much of the blame for everything that happened on his study coordinators -- again, without providing evidence to support the assertion. While he was the beneficiary of the illegal activity, he maintained that it was the salaried employees working for him who devised the frauds, often without his knowledge. The information provided by Dr. Fiddes has not resulted in any additional investigations.

Despite his refusal to accept the blame, Dr. Fiddes was anguished at being labeled a criminal. In a letter pleading for mercy that he sent last year to Federal District Judge Robert M. Takasugi, he described his torment. "My family has had to endure the humiliation of seeing a husband and father sink from being a widely respected community member to now being visualized as nothing more than a common crook," Dr. Fiddes wrote. "My mother often said, 'The only thing in life that is important is to be able to hold your head up high.' I now know what that means."

The Career

From Family Doctor To Drug Researcher

Robert Fiddes always wanted to be a skater. As a teen-ager in his native Vancouver, British Columbia, he rose most mornings before dawn, walking to a chilly ice arena for his 5 A.M. practice. The hard work paid off; he often told of winning Canada's junior figure skating championship, a victory that set him on the path to going professional.

But when the time came to choose between a career as a figure skater or enrolling in a university, young Robert Fiddes took the academic path. And there he showed that same drive, gaining acceptance to medical school at the University of British Columbia after just three years in college, according to his curriculum vitae.

In 1970, at 25, Dr. Fiddes earned his medical degree and, with his new wife, Rebecca, came to Long Beach, Calif., for a job as a hospital intern. He went on to join a medical partnership, but in 1981 opened his own practice in Whittier with a medical assistant, LaVerne Charpentier, in a converted house with an awning and flower garden. It was the perfect image for an old-time family doctor, and the practice blossomed.

Dr. Fiddes's wife would later write of those early days in a letter to the judge who sentenced her husband. "His patients adored them and showered the office with everything from home-baked cookies to hand-crocheted dolls," she wrote. "Both Rob and Laverne worked long and hard to provide his patients with the best care."

Eventually, Dr. Fiddes formed a group made up of several family doctors in the area. But by the late 1980's, an obstacle emerged that Dr. Fiddes was unable to sidestep. Managed care was sweeping California, and Dr. Fiddes chafed at the new rules. "He felt his hands were tied in performing whatever tests were necessary to assist in the proper diagnosis of the patient," Mrs. Fiddes wrote in her letter. Patients "felt equally frustrated with the new system."

Growing restless, he decided to pursue a law degree, attending night school. In 1987, he passed the California state bar exam.

But by then, the medical profession had changed so radically that an entirely new specialty presented itself: Doctors were testing the safety and effectiveness of new drugs for pharmaceutical companies, using their patients as subjects. Recognizing the opportunity to get away from managed care, Dr. Fiddes jumped at the chance.

His new clinical-trials business grew rapidly. Dr. Fiddes appointed Ms. Charpentier as his first full-time study coordinator, and raided a private research firm in the area, California Clinical Trials, to build his staff. He began to dream of eclipsing his biggest rivals and taking his new enterprise public, at times doodling his ideas for a corporate logo onto pads of paper.

As the business grew, former employees said, a pattern soon emerged. Dr. Fiddes would meet with patients in his first-floor office, then refer them to the study coordinators on the second floor. Often, the patients who arrived there felt reluctant to take part in the trials.

"They were pushed to go up there," said Susan Lester, the former study coordinator who blew the whistle on Dr. Fiddes. "They often would say, 'I don't want to participate in this, but I don't want to make him mad.' "

In the early days, Ms. Lester and other coordinators would tell wavering patients to take their time, perhaps by sleeping on the idea, before signing an agreement to participate. But Dr. Fiddes and Ms. Charpentier, who also declined interview requests, quickly put an end to such solicitousness.

"I was told that it was a big mistake to let them think about joining," Ms. Lester said. "They said, 'You don't tell them they have any choice about it. You put them in.' "

The Fraud

Falsifying Records, Endangering Patients

Kimberly Carlon's interviews for a job at the Southern California Research Institute had been going well. She had only one more hurdle to clear: speaking to Dr. Fiddes himself. If he approved of her, Ms. Carlon, a certified respiratory therapist, would become the research site's latest study coordinator. Sitting in front of Dr. Fiddes's desk in early 1996, she listened as he described a hypothetical situation. Suppose, he said, that a patient was available for a study, but was taking medication prohibited by the study protocol. The answer seemed obvious, Ms. Carlon replied: she would send the patient on his way.

Well, Dr. Fiddes told her, that was not the way he did things. At the Southern California Research Institute, he said, the patient would be entered into the trial; that would require the center to falsify records so that the violation of study rules could be hidden.

Ms. Carlon got the job. But she would later describe her discussion with Dr. Fiddes as the first moment she should have realized something was wrong.

Like every other study coordinator who passed through Dr. Fiddes's research center, Ms. Carlon found herself being pushed to break the rules. When she ran a 1996 study for a new asthma inhaler sponsored by Fisons, a British drug maker, she found a patient who had been enrolled even though she had an incurable lung disease that should have disqualified her. When a monitor hired by Fisons asked to see the patient's medical chart, Ms. Carlon approached Delfina Hernandez, a more senior employee, and asked what to do.

Ms. Hernandez quickly fetched the patient's medical chart, and pulled out every page that made reference to the lung disease. Then, according to investigative documents, she turned the remaining records over to the monitor. The violation went undetected.

Ms. Hernandez, who later pleaded guilty to fraud, declined to comment.

Again and again, study coordinators were instructed by Dr. Fiddes and his top aide, Ms. Charpentier, to ignore the requirements of the drug studies. The rules called for excluding smokers from an asthma study? The coordinators were told to put the smokers in anyway, and not mention their habit in the medical records. A certain blood pressure was required for patients to participate in a hypertension study? Then the coordinators were expected to write that level into the chart, regardless of the truth. Patients' medical records contained health histories that precluded them from participating in a test? Then the offending pages were ripped out and destroyed, and the patients placed on the experimental medication despite the dangers.

Over time, the frauds orchestrated by Dr. Fiddes grew ever more audacious. Eventually, according to Government documents, it was not just the records that were being falsified. Instead, medical tests were rigged -- and at times, patients simply invented. Outside monitors reviewed the documentation, but since there were real lab records for the rigged tests, they had no clue that they were being deceived.

The office refrigerator became the source of human bodily fluids that met the requirements of various studies. A jug of urine was often found there on Monday mornings, provided by Carol Rose, an employee. Ms. Rose's urine contained high levels of protein -- just the trait patients needed to qualify for certain studies. Dr. Fiddes paid Ms. Rose $25 each time she collected her urine and brought it to the office, where over time it was divvied up among specimen cups labeled with other people's names and presented for testing.

The refrigerator also proved useful when the research center was conducting studies on hormone replacement therapy for menopausal women. The studies required women with blood serums that showed low levels of estrogen and high levels of follicle-stimulating hormone -- signs that a woman is going through menopause. To make sure that the patients' tests qualified, Dr. Fiddes sent out a memo specifying the hormone levels required for the study. "We need some serum that scores these numbers in the frig at all times," he wrote.

Another study on an antibiotic required that patients have a certain type of bacteria growing in their ear. No problem for Dr. Fiddes. He bought the bacteria from a commercial supplier and shipped them to testing labs, saying they had come from his patients' ears.

Dr. Fiddes's coordinators, paid bonuses for recruiting patients into studies, soon began improperly enrolling themselves and members of their families. Often, names were changed to avoid detection by drug company monitors. At times, family members took part in several studies at once -- a violation of the rules because studies require that participants not be taking other medications, so that the data obtained relate only to the drug under study.

Employees "were running around doing E.K.G.'s on each other, if the patient couldn't pass," said Sloan A. Bergman, a former study coordinator who quit working for Dr. Fiddes after less than a year because of ethical concerns. "I wasn't happy, but I needed a job."

Yet all the while, there were constant reminders that the true cost of the frenzied drug testing was being borne by sick and vulnerable patients.

In the summer of 1995, the research institute began work on a study of Cozaar, a hypertension medication sponsored by Merck & Company. Among the patients enrolled by Dr. Fiddes was Arlene Roberts, a 70-year-old woman with high blood pressure. Instead of dropping, her blood pressure rose dangerously when she took the drug. Dawn Simons, the study coordinator, became alarmed and sent Ms. Roberts to see Dr. Fiddes. Rather than taking her out of the study, Dr. Fiddes prescribed two other hypertension drugs. The triple dosage not only violated the study rules, it made it impossible to gauge the effect of Cozaar.

A few days later, Ms. Roberts returned. Her face was bruised, her speech was slurred and she had trouble walking. She told Ms. Simons that she had passed out over the weekend while bathing. Ms. Simons took her pulse and found that her heart was barely beating -- a result, the coordinator thought, of bombarding her body with hypertensive drugs. Worried that Ms. Roberts was headed toward cardiac arrest, Ms. Simons asked Ms. Lester, her fellow study coordinator, for assistance. The two helped Ms. Roberts, who by then could barely walk, to Dr. Fiddes's office.

''He said, 'It's no big deal. She's probably making more of it than it really is,' '' Ms. Lester recalled in a recent interview.

Ms. Simons, dismayed at what was happening, thought Ms. Roberts should be dropped from the study. But Dr. Fiddes refused, keeping her on the medications for several more weeks. Ms. Roberts was soon seeing another doctor in a hospital for the problems that emerged during the study. Ms. Simons, the study coordinator, resigned from her job, but not before surreptitiously copying all the medical records and turning them over to Ms. Roberts in case she wanted to bring a lawsuit. Ms. Roberts, who recovered at the hospital, never sued.

Dr. Fiddes received payment in full from Merck -- his reward for keeping Ms. Roberts in the study through its completion.

Avoiding Detection

The F.D.A. Ignores An Early Warning

Ilse Beverly finally decided that Dr. Fiddes had to be stopped. While working for him for five years handling laboratory tests like blood work, Ms. Beverly had seen signs of his willingness to cheat on drug studies. And so in January 1995, almost immediately after leaving her job, Ms. Beverly telephoned investigators with the Food and Drug Administration.

She reported her own experiences, such as the time in 1990 that Dr. Fiddes had asked her -- without explaining why -- to find a way to alter lab values in urine tests. She also provided the names of study coordinators who knew that testing data were being manipulated to enroll larger numbers of patients. With her revelations, the Government had its first solid lead on what was happening in Dr. Fiddes's office fully 17 months before Ms. Del Valle exposed his crimes to an F.D.A. auditor. Investigators wrote memos about Ms. Beverly's allegations, and forwarded them from Los Angeles to the clinical investigations branch of the F.D.A.

There, the memos were filed away. No investigation was begun.

Brad Stone, a spokesman for the F.D.A., said that, because aspects of the case have not been finished, the agency could not comment at this time.

Dr. Fiddes had always found it easy to elude detection by the crews of company monitors and Government auditors that visited his offices, even when his employees spelled out their suspicions about what was happening. It was not that he was particularly adept at dodging their questions; rather, they seemed reluctant to challenge such a prominent figure in the drug-testing business. ''This business can be run on words, and I have learned the words,'' Dr. Fiddes wrote in a 1995 memo. '' 'We have no problems' is our motto, and tell this to every monitor.''

When Dr. Fiddes's efforts to enroll patients were thwarted by system safeguards intended to insure accurate test data, he often found ways around the problem.

In a 1995 study of an experimental pain reliever for arthritis called PHZ 136 that was sponsored by the Zambon Corporation, Dr. Fiddes faced a particularly difficult impediment. The patients were supposed to have arthritis of the knee, as verified by X-rays.

Dr. Fiddes tried to recruit patients. Again and again, he sent their X-rays to an independent radiologist for review. And almost every time the answer came back the same: The patient did not have arthritis, and so did not qualify for the study. Frustrated, Dr. Fiddes told the coordinator of the study, Ms. Lester, to look through his medical files for patients with arthritis of the knee. Then, he said, she should offer each of those patients $25 to come in and get multiple X-rays, which he could substitute for the X-rays of patients who did not qualify. But Ms. Lester drew the line, and refused.

The ever-resourceful Dr. Fiddes found a way around that obstacle, however. Through his staff, he got in touch with the project manager at Pharmaceutical Product Development Inc., which was managing the study for Zambon, and asked a question: Because he was a doctor, couldn't he just interpret his patients' X-rays himself, rather than send them to a certified radiologist?

The company was happy to oblige. Researchers "may interpret knee X-ray films obtained on candidates," Julia Dixon, the project manager, wrote in a letter to Dr. Fiddes. "There is no need for a radiological consult."

From that moment on, Dr. Fiddes had no trouble finding patients who qualified for the study. "That kind of opened it up for him right there and then," Ms. Lester said. "Everyone understood that if he was going to read the X-ray, he was going to lie."

Not long afterward, Dr. Fiddes received a letter from one of the testing company's study monitors. "CONGRATULATIONS on meeting your enrollment deadline!" the monitor, Cheryl Grant, wrote in a letter dated Feb. 19, 1996. "I performed a 100 percent source document verification, and found no outstanding issues."

Through Pharmaceutical Product Development, a testing company, Dr. Fiddes was paid $45,268 for his effort in the Zambon study. The company never detected his fraud. Zambon declined to comment, citing confidentiality of the study, as did Pharmaceutical Product Development. But Nancy Zeleniak, a spokeswoman for the testing company, said its monitoring was of the highest quality. "We have standard operating procedures for detecting fraudulent or fabricated data," she said. "We are helping to set standards in the industry."

Another company came closer to putting him on the spot. Several former coordinators for Dr. Fiddes said they had reported his unethical conduct to Pat Pryor, an independent study monitor working with Pfizer Inc. Tipped off to the discrepancies, Ms. Pryor sharply challenged Dr. Fiddes and his staff in her reviews of their paperwork.

Dr. Fiddes chafed at the challenges, feigning outrage. "Our integrity and reputation for performing high-quality clinical trial work has been injured, and we are justifiably upset," Dr. Fiddes wrote in a July 1995 letter to Pfizer, complaining about Ms. Pryor's demands. He insisted Pfizer "have a new monitor assigned to our site immediately."

Not long afterward, Dr. Fiddes announced the news at a staff meeting: Pat Pryor would not be returning to monitor the Southern California Research Institute.

Pfizer said that the company replaced monitors if there seemed to be a conflict. "In order to insure the most objective and best monitoring, we generally recommend that if there is personal conflict, and no certainty of irregularities, that a new neutral person is assigned to review all of the data," said Betsy Raymond, a spokeswoman for Pfizer.

But in the Fiddes case, that policy did not improve the monitoring. "We have an extensive system of checks and balances," Ms. Raymond said. "Even with all of that, we didn't uncover the fraud."

Why was Dr. Fiddes able to fool the monitors so easily? Because the oversight system is mostly designed to catch errors, not fraud. To protect patient confidentiality, monitors are forbidden even to know the names of test subjects, meaning that no spot-checks are ever performed by the companies to make sure that researchers are not making up lab values or inventing patients.

But Dr. Fiddes's luck in avoiding detection would not hold. By May 1996, more than half a dozen study coordinators -- including Ms. Simons and Ms. Bergman -- resigned, fearful that the fraud would cost them their nursing licenses or certifications. Ms. Lester likewise decided she could take no more, and wrote a letter to Dr. Fiddes declaring that she would no longer participate in fraudulent, unethical work.

A response came quickly. Ms. Lester was ordered to clean out her desk immediately, and was escorted from the building. On her way out the door, she bumped into Kathryn Davis, another Fiddes employee. With tears in her eyes, Ms. Lester made Ms. Davis a promise.

"She told me before she left that she was going to bring Dr. Fiddes to his knees," said Ms. Davis, a former employee. "I had no idea that she meant it seriously."

The Cover-Up

'You MUST Be Able To Dump Your Files'

Alan Knox, the chief financial officer of the research center, was working in his office in the summer of 1996 when its chief operating officer burst in. The officer, Elaine Lai, demanded that Mr. Knox pull a series of invoices documenting payments to an employee, Carol Rose.

Mr. Knox fished the invoices from a filing cabinet. As he read them, he grew concerned. Written clearly across the $25 invoices were the words "urine sample." For the first time, he was seeing the evidence that Ms. Rose was being paid to substitute her own urine for that of patients.

Wary of what was happening, Mr. Knox copied the invoices, and kept the originals. As he handed the copies to Ms. Lai, he asked her and Ms. Hernandez, the longtime senior employee of Dr. Fiddes, what was going on. Well, came back the response, apparently Susan Lester had gone to the F.D.A., and worse, was contacting other former coordinators and trying to persuade them to talk to the Government about the way Dr. Fiddes conducted his research.

"I remember inquiring with Delfina and Elaine and saying, 'What's the big deal?' " Mr. Knox said in a recent interview. "They looked at me,

they looked at each other and said, 'We have to tell him the truth.' " As he listened to them recount the trickery that had taken place at the institute, he said, "I was just taken aback by the level of fraud."

His first thought, he said, was that Dr. Fiddes and his top aides should confess everything to the F.D.A. But unknown to him, they were at that very moment planning a cover-up that would involve destroying incriminating documents and manufacturing new ones that might place the blame for any problems on Ms. Lester.

Dr. Fiddes was most concerned about the urine substitution, out of fear that Ms. Rose would talk, according to notes of investigator interviews. So, in August 1996, he called a meeting at the Hilton Hotel in Whittier with Ms. Lai, Ms. Hernandez and his longtime assistant, Ms. Charpentier.

To solve the Carol Rose problem, Dr. Fiddes told the group, he would create a bogus medical chart and false patient history for her. If asked, he would say that urine had been collected as part of her medical treatment.

The following Saturday, Ms. Lai called a meeting for what she called "chart review." The actual mission was to go through the medical charts and destroy any evidence of wrongdoing.

Days later, on Aug. 21, Ms. Lai called for another meeting for strategic planning. In a memo to Dr. Fiddes, Ms. Charpentier and Ms. Hernandez, she made clear the need to move quickly.

"F.D.A. is busting down our door on Monday," Ms. Lai wrote. "You MUST be able to dump your files to your car when F.D.A. knocks."

Ms. Lai added in the letter that they had to agree to scripted responses to all questions the Government might ask.

As Dr. Fiddes and his allies were secretly working on their cover-up, Mr. Knox was reaching out to regulatory experts who he thought could help the company in its talks with the F.D.A. He got in touch with Gretchen McKelvey, a quality assurance consultant for clinical trials, who was quickly hired to help out. Ms. McKelvey was stunned by the magnitude of the fraud she discovered at Dr. Fiddes's office. But even more incomprehensible was the blase attitude Dr. Fiddes demonstrated as he calmly informed her of his cover-up plans.

"I explained to him that what had happened here was considered criminal, and that he could be prosecuted for conspiracy and fraud," Ms. McKelvey said in an interview. "Dr. Fiddes replied that they were going to blame Susan Lester for all of the problems, and he was going to say he had no knowledge of what was going on."

About that time, Ms. McKelvey learned that Dr. Fiddes had moved all of the patient records off site. When she asked where they were, she said, he replied that they were in storage. Days later, when she pressed for them again, Dr. Fiddes told her the records had been lost.

"I was starting to get really scared," she said. "I don't like to be messed with."

As the situation deteriorated, Ms. McKelvey decided the situation was too big to handle alone, and required someone with more expertise in dealing with the Government. She sought advice from Michael Hamrell, a consultant who specialized in the F.D.A. Mr. Hamrell arrived at the research site for a briefing from the company's top executives, including Dr. Fiddes and Mr. Knox. They made no bones about all the protocol violations they had committed. Why would Dr. Fiddes be so open? Because, as Mr. Hamrell learned quickly, he still believed that he could outsmart the system.

"He told me that he knew the law better than the F.D.A., and that the F.D.A. couldn't touch him," Mr. Hamrell said. "He told me he was a lawyer, and he wasn't responsible."

Many of those who worked for him, like Mr. Knox and Ms. McKelvey, saw the writing on the wall and resigned soon after being hired. But others who for years had accepted Dr. Fiddes's repeated assurances that everyone in the industry did the same things were shaken and agonized about whether to confess.

"I want to spill my guts, but what is going to happen to me and my future?" Delfina Hernandez, one of Dr. Fiddes's top aides, wrote in her diary as investigators closed in. "God forgive me if you think I did wrong, and punish me if I did anything to hurt these patients."

She soon found out what would happen to her future. On Feb. 16, 1997, teams of Federal agents swarmed into the Southern California Research Institute's office. The entire staff was ordered to move to the front of the building, as the agents seized box after box of documents. One agent with a video camera filmed every employee's face for use in future identifications.

With employees facing such intimidating law enforcement tactics, cracks began to emerge in the conspiracy to lie to investigators. Ms. Hernandez was the first to decide to provide evidence to the Government, and the other dominoes quickly fell. By September 1997, Dr. Fiddes, Ms. Hernandez and Ms. Charpentier agreed to plead guilty. Ms. Lai pleaded guilty soon afterward.

Now, with Dr. Fiddes compelled to cooperate as part of his plea agreement, the Government hoped to learn more from him that would help in the battle against research fraud. On Oct. 10, at 10:30 A.M., Dr. Fiddes met for an interview with William Leitner and Hetal Sutaria of the F.D.A.

For five hours, the agents grilled Dr. Fiddes. He told them that fraud was rampant in the research industry. He named names of doctors he suspected of engaging in practices similar to his own. And he described some telltale signs that should raise suspicions of possible fraud.

But, the investigators asked, what evidence of fraud is there in the records reviewed by monitors and the Government? What could the watchdogs have seen that would have allowed them to detect his fraud?

Nothing, Dr. Fiddes replied. Had it not been for a disgruntled former employee, he would have still been in business.

Editor's Note: *July 2, 1999, Friday An article on May 17 described fraudulent trials of new drugs by Robert Fiddes, a California doctor who operated a company, now defunct, that he called the Southern California Research Institute. Dr. Fiddes had no connection to another company of the same name in Los Angeles, a nonprofit corporation that has conducted research on traffic safety since 1973.*

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF KANSAS

UNITED STATES OF AMERICA, Plaintiff, v. LISA SHARP, and WAYNE SPENCER, M.D., Defendants.	)	No. 11-40042-01-02-RDR Count 1: 18 U.S.C. § 371 Counts 2-4: 18 U.S.C. § 1341 Count 5: 21 U.S.C. § 331(e) Counts 1-5: 18 U.S.C. § 2

INDICTMENT

The Grand Jury charges:

At all material times:

INTRODUCTION

1. From in or about January, 2010, through in or about May, 2010, defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, while employed at Lee Research Institute, were involved in a conspiracy and scheme to defraud Schering/Plough, a subsidiary of Merck ("Schering/Plough") in relation to a clinical drug trial. Specifically, defendants falsified study data to remain in the clinical drug trial and receive monies from Schering/Plough.

2. Schering/Plough was a pharmaceutical company engaged in developing, testing, and marketing pharmaceutical products, including a sublingual

tablet developed for the treatment of allergies, namely ragweed-induced rhino conjunctivitis.

3. Under the Federal Food, Drug, and Cosmetic Act ("FDCA") and its implementing regulations, Schering/Plough, the drug sponsor, had to apply to the United States Food and Drug Administration ("FDA"), an agency of the United States, for approval to market their sublingual tablet. As a drug sponsor, Schering/Plough was required to demonstrate, through clinical investigations, the safety and effectiveness of the sublingual tablet before the FDA would approve it for human use or consumption. Clinical investigations are experiments or studies in which the sublingual tablet was administered to a human group. The FDA examines the results, design, and conduct of the clinical studies in deciding whether the sublingual tablet should be approved for marketing.

4. Before beginning the clinical study, the FDA required Schering/Plough to provide the FDA a detailed investigation plan known as the "study protocol." The study protocol contained information about how the clinical study would be conducted, where studies would be done and by whom, how the drug's safety would be evaluated, and what findings would require the study to be changed or halted.

5. Schering/Plough hired clinical investigators to carry out the actual clinical studies of the drug on human subjects. Participating clinical investigators signed FDA Forms 1572, committing to conduct the study in accordance with the study protocol, to personally conduct or supervise the investigation, and to comply with FDA regulations. The FDA required that truthful and correct information be provided in order to evaluate the safety and performance of a drug before it approved the drug's use by certain groups of individuals.

6. In or about July 2009, Schering/Plough chose Lee Research Institute to perform a clinical study known as "A 28-Day Study Evaluating the Safety of Ragweed (*Ambrosia artemisiifolia*) Sublingual Tablet (SCH 39641) in Adult Subjects 50 years of age and Older with Ragweed-Induced Rhino conjunctivitis" ("the clinical study").

7. Defendant **WAYNE SPENCER, M.D.**, a licensed medical doctor practicing medicine in the District of Kansas, was the Principal Investigator for the clinical study.

8. Defendant **LISA SHARP** was the Lead Clinical Research Coordinator for the clinical study. Additionally, defendant **LISA SHARP** was the Director of Clinical Trials for Lee Research Institute.

9. Defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, agreed to conduct the study in strict compliance with the criteria set forth in the study protocol.

10. According to Section 7.3.1 of the study protocol, "each subject must be 50 years of age and older."

11. According to Section 7.3.2 of the study protocol, "a subject who is a member or a family member of the personnel of the investigational or sponsor staff directly involved with this trial" are excluded from the study. In other words, employees of Lee Research Institute were excluded from the study.

12. The clinical study required that Lee Research Institute enroll eight eligible participants.

COUNT 1 – CONSPIRACY

13. The Grand Jury incorporates by reference Paragraphs 1 through 12 as though fully restated and re-alleged herein.

14. From in or about January 2010, through in or about May 2010, the exact dates being unknown to the Grand Jury, in the District of Kansas, the defendants

LISA SHARP
and
WAYNE SPENCER, M.D.,

knowingly and willfully combined, conspired, confederated, and agreed with each other and with others, both known and unknown to the Grand Jury:

(a) to commit mail fraud, in violation of Title 18, United States Code, Section 1341;

(b) to violate the Food, Drug and Cosmetic Act by failing to prepare and maintain records required under 21 U.S.C. § 355(i) and 21 C.F.R. § 312.62(b), with intent to defraud and mislead, in violation of Title 21, United States Code, Section 331(e); and

(c) to defraud the United States and departments and agencies thereof, namely, the Food and Drug Administration, by impairing, impeding and obstructing by craft, trickery, deceit, and dishonest means, its lawful and legitimate function of regulating drugs.

Purpose of the Conspiracy and Scheme

15. A purpose of the conspiracy and scheme was to make money for Lee Research Institute, the defendants' employer, so that Lee Institute would remain in business and the defendants would remain employed.

Manner and Means

16. Defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, and others used the following manner and means in furtherance of the continuing

conspiracy and scheme to defraud. In so doing, defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, and others, at times, used and perverted lawful conduct to further the conspiracy and scheme.

17. It was a part and object of the continuing conspiracy and scheme to defraud that defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, reported that all eight study subjects for the clinical study were qualified to participate in the study, when they knew that two subjects were not qualified because of age and employment.

18. It was a part and object of the continuing conspiracy and scheme to defraud that defendant **LISA SHARP,** in direct violation of the protocol, had two employees at Lee Research Institute, namely the Regulatory Coordinator and another Clinical Research Coordinator, complete enrollment forms to be clinical study participants using the false names of Kathryn F. Cline and Elizabeth S. Armstrong.

19. It was a part and object of the continuing conspiracy and scheme to defraud that defendant **LISA SHARP,** in direct violation of the protocol, had two employees at Lee Research Institute, namely the Regulatory Coordinator and another Clinical Research Coordinator, enroll as clinical study participants, even though both were under the age of 50. Defendant **LISA SHARP** provided the

employees with false birth years to use for the enrollment forms and to make it appear that they met the protocol requirement of being 50 years of age or older.

20. It was a part and object of the continuing conspiracy and scheme to defraud that defendant **LISA SHARP** approved payments to the two employees for participating in the clinical study.

21. It was a part and object of the continuing conspiracy and scheme to defraud that defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, knowing that two employees were falsely enrolled in the clinical study, signed multiple forms and records, all of which were documents required to be created and maintained as a part of the clinical study.

Overt Acts

22. In furtherance of the continuing conspiracy and scheme to defraud, and to accomplish their purposes and objectives, one or more of the co-conspirators committed in the District of Kansas the following overt acts, among others:

a. Each of the allegations set forth in Counts 2-5 is incorporated and realleged as though restated herein, as an individual overt act done in furtherance of the conspiracy.

b. On or about January 8, 2010, two Lee Research Institute employees enrolled as participants in the clinical study under false names and using false dates of birth. Neither employee was 50 years of age or older.

c. On or about January 8, 2010, defendant **LISA SHARP** informed defendant **WAYNE SPENCER, M.D.**, that two employees had enrolled as participants in the clinical study.

d. On or about January 8, 2010, defendant **WAYNE SPENCER, M.D.**, signed multiple documents for the enrolled employees, including page 6 of the Screen Visit Forms, indicating that he had performed physical examinations on the two employees, when he had not performed any physical examinations of these two employees.

e. On or about January 8, 2010, defendant **LISA SHARP** signed multiple documents for the enrolled employees, including documents that falsely stated their dates of birth.

f. On or about January 11, 2010, defendant **WAYNE SPENCER, M.D.**, signed page 5 of the Screen Visit Forms for both enrolled employees, indicating that the patients met the inclusion/exclusion criteria, when he knew that they did not.

g. On or about February 22, 2010, defendant **WAYNE SPENCER, M.D.**, signed FDA Form 1572, indicating that he had conducted the clinical study in accordance with the protocol.

h. During the course of the clinical study, defendant **LISA SHARP** made sure that the two employees had office visits when the Executive Director was at lunch, to conceal from her the fact that the clinical study had two ineligible participants.

23. The foregoing is in violation of Title 18, United States Code, Sections 371 and 2.

COUNTS 2-4

24. The Grand Jury incorporates by reference Paragraphs 1 through 23 as though fully restated and re-alleged herein.

25. On or about the dates detailed below, in the district of Kansas, defendants

LISA SHARP
and
WAYNE SPENCER, M.D.

knowingly and intentionally devised a scheme to defraud, and for the purpose of executing the scheme to defraud, and attempting to do so, deposited and caused to be deposited in any post office or authorized depository for mail matter, any matter

or thing whatever to be sent or delivered by the Postal Service, and deposited and caused to be deposited any matter or thing whatever to be sent or delivered by any private or commercial interstate carrier, and took and received from the Postal Service and any private or commercial interstate carrier any such matter or thing, namely the following checks issued to Lee Research Institute in payment for the clinical study:

Count	On or about Date	Check Number	Amount
2	February 26, 2010	4628769	20,877.00
3	April 9, 2010	4639491	7,606.80
4	May 10, 2010	4645963	3,604.80

26. The foregoing is in violation of Title 18, United States Code, Sections 1341 and 2.

COUNT 5 – FDCA VIOLATION

27. The Grand Jury incorporates by reference Paragraphs 1 through 23 as though fully restated and re-alleged herein.

28. FDA regulations imposed the following specific responsibilities on defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, in regards to the clinical study: to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the

investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

29. The study protocol also imposed specific responsibilities on defendants **LISA SHARP** and **WAYNE SPENCER, M.D.**, in regards to the clinical study. The defendants were required to:

a. maintain records and data during the trial in compliance with all applicable legal and regulatory requirements; and

b. maintain source documents that support each data point, and retain such source documents for review by the sponsor or a regulatory agency.

30. Under Title 21, United States Code, Section 331(e), it is unlawful for any person, with intent to defraud and mislead, to fail to establish or maintain any record, or make any report required under Title 21, United States Code, Section 355(i), including those records required under 21 C.F.R. §§ 312.62(b) and 312.66.

31. Beginning in or about January 2010, and continuing through in or about May 2010, in the district of Kansas, defendants

LISA SHARP
and
WAYNE SPENCER, M.D.,

with intent to defraud and mislead, failed to prepare and maintain records required under 21 U.S.C. § 355(i) and 21 C.F.R. § 312.62(b), namely, adequate and accurate case histories on each individual administered the investigational drug, in that the defendants falsified the birth dates of two participants; falsely indicated that physical examinations had been performed, when they had not been performed; and indicated on required forms that the two participants met the inclusion criteria and had no reasons for exclusion, when the defendants knew that the participants did not meet the inclusion criteria of age and should have been excluded as employees of the research facility conducting the clinical study.

32. The foregoing is in violation of Title 21, United States Code, Section 331(e), 333(a)(2), and Title 18, United States Code, Section 2.

A TRUE BILL.

Dated: June 1, 2011

s/ Foreperson
FOREPERSON

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(It is requested that trial of the above captioned case be held in Topeka, Kansas.)

Writing An Effective 483 Response

5th Annual FDA and the Changing Paradigm for HCT/P Regulation
University of Rhode Island and Pharma Conference
Las Vegas, NV, January 2009

Anita Richardson
Associate Director for Policy
Office of Compliance & Biologics Quality

U.S. Department of Health and Human Services
Food and Drug Administration

A Fable

A well-reasoned, complete, and timely 483 response is in your best interest.

The 483 response

- There is no regulatory requirement to respond to the 483….

…..however, it's in your best interest to respond in writing.

Writing an effective 483 response Topics to be covered:

- Regulatory framework and FDA policies and procedures for the FDA 483;
- Four reasons for submitting a well-reasoned, complete, and timely 483 response;
- Eight suggestions for an effective 483 response.

Form FDA 483 Inspectional Observations

- Under what authority does FDA issue 483s?
  - "The observations of objectionable conditions and practices listed on the front of this form are reported:
    1. Pursuant to Section 704(b) of the FFD&C Act
    2. To assist firms inspected in complying with the Acts and regulations enforced by the FDA"

Form FDA 483 Inspectional Observations

- Clarification:
  - What is a Form FDA 483?
  - What is it not?

Form FDA 483 Inspectional Observations

- List of inspectional observations
- 483 language
  - *"This document lists observations made by the FDA representative during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance."*

(Form FDA 483 & FDA Investigations Operations Manual (IOM) 5.2.3.1.4 http://www.fda.gov/ora/inspect_ref/iom/)

FDA's expectations during an inspection

- *"…investigators should make every reasonable effort to discuss all observations with management… as they are observed, or on a daily basis to minimize surprises, errors, and misunderstandings when an FDA 483 is issued."*
- IOM 5.2.3

FDA's expectations during an inspection (2)

- *"Industry may use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made…"*
  - IOM 5.2.3

FDA activities following the inspection

- Investigators prepare the Establishment Inspection Report (EIR) & recommend classification of the inspection
- Supervisory review
- Classification of inspection: NAI, VAI, OAI
- If OAI, referral to district's Compliance Branch for further review & action

Why submit a 483 response?

Four reasons for submitting a well-reasoned, complete, and timely 483 response

1. Could possibly mitigate an FDA compliance decision for further action, e.g. untitled letter, Warning Letter

Four reasons for submitting a well-reasoned, complete, and timely 483 response

1. (cont)

- "As a general rule, a Warning Letter should not be issued if the agency concludes that a firm's corrective actions are adequate and that the violations that would have supported the letter have been corrected."
- Regulatory Procedures Manual, http://www.fda.gov/ora/compliance_ref/rpm/pdf/ch4.pdf

Four reasons for submitting a well-reasoned, complete, and timely 483 response

2. Demonstrates to the FDA (and other stakeholders) an understanding and acknowledgement of the observations

Four reasons for submitting a well-reasoned, complete, and timely 483 response

3. Demonstrates to the FDA (and other stakeholders) a commitment to correct, i.e. the intent to voluntarily comply

Four reasons for submitting a well-reasoned, complete, and timely 483 response

4. Establishes credibility with FDA

Suggestions for addressing 483 observations

Following an Inspection – Suggestions:

- Assess each observation
  - Focus on specifics
  - Focus on system-wide implications
  - Focus on global implications
  - *Consider affected products*
  - Consider root-cause analysis
  - Focus on the regulatory requirement(s) associated with the observation

Following an Inspection – Suggestions (cont):

- Develop action plan to achieve immediate, short-term, and long-term correction and to prevent recurrence
- Know when to seek outside assistance

Eight suggestions for an effective 483 response

Eight suggestions for an effective 483 response:

1. Include a commitment/statement from senior leadership
2. Address each observation separately
3. Note whether you agree or disagree with the observation

Eight suggestions for an effective 483 response:

4. Provide corrective action accomplished and/or planned; tell FDA the plan
   - Be specific (e.g. observation-by-observation)
   - Be complete
   - Be realistic
   - Be able to deliver what you promise
   - Address affected products

Eight suggestions for an effective 483 response:

5. Provide time frames for correction
6. Provide method of verification and/or monitoring for corrections
7. Consider submitting documentation of corrections where reasonable & feasible
8. BE TIMELY

To summarize

- There is no regulatory requirement to respond to the 483….

…..however, a well-reasoned, complete, and timely 483 response is in your best interest.

Contacts For CBER Assistance:

WWW.FDA.GOV/CBER

- Email CBER:
  - –Manufacturers: matt@cber.fda.gov
  - –Consumers, health care
  - –octma@cber.fda.gov
- Phone:
  - –+1-301-827-1800

“The safest way to double your money is to fold it over once and put it in your pocket”

Kin Hubbard

GxP Process Management Software

master™ CONTROL

White Paper:

Ten Most Common Reasons for FDA 483 Observations and Warning Letter Citations

Most FDA violations involve one of the following:

- Not having procedures in a regulated area that conform to FDA regulations;
- Having procedures that conform to FDA regulations, but not following them; or
- Having procedures that conform to FDA regulations and following them, but not having adequate documentation to show that you're following them.

By sending an FDA-483 Obs. or Warning Letter, the FDA is communicating to a medical device company that its procedures are (or may be) inadequate in a specific regulated area for one of the above reasons.

At a recent Intermountain Biomedical Association workshop held in Lehi, Utah, Barbara Cassens, Director of the FDA's San Francisco District Office, identified ten specific FDA regulated areas in which medical device companies (as of July 30, 2007) most commonly receive FDA-483 Observations and Warning Letter citations.

1. Complaint Handling Procedures are Inadequate

Section 21 CFR 820.198(a) states that a medical device manufacturer must maintain complaint files, as well as procedures for receiving, reviewing, and evaluating complaints. Such procedures must ensure that:

- All complaints are processed in a uniform and timely manner;
- Verbal complaints are documented upon receipt; and
- Complaints are evaluated to determine whether the complaint represents an event that must be reported to the FDA.

The regulation further requires that complaint files and procedures be contained "within a formally designated unit."

2. Corrective and Preventive Action (CAPA) Procedures are Inadequate

Under 21 CFR 820.100(a), manufacturers of medical devices must establish and maintain procedures for corrective and preventive actions, including procedures for:

- Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology must be employed where necessary to detect recurring quality problems.
- Investigating the cause of nonconformities relating to products, processes, and the quality system.
- Identifying the action(s) needed to correct and prevent recurrence of nonconforming products or other quality issues.
- Verifying or validating a corrective and preventive action to ensure that it is effective and does not adversely affect the finished device.

- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.

- Ensuring that information related to quality problems or a nonconforming product is disseminated to those directly responsible for assuring the quality of the product or preventing problems.

- Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

3. Written Medical Device Reporting (MDR) Procedures are Inadequate

Section 21 CFR 803.17 stipulates that manufacturers, user facilities, and importers of medical devices must develop, maintain, and implement written medical device reporting (MDR) procedures for internal systems. The procedures must provide:

- Timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements;

- A standardized review process or procedure for determining when an event meets the criteria for MDR reporting; and

- Timely transmission of complete medical device reports to manufacturers or the FDA (or both, if required).

In addition, FDA regulation 21 CFR 803.17 requires manufacturers, user facilities, and importers of medical devices to establish documentation and recordkeeping requirements for:

- The information that was evaluated to determine whether an event was reportable;

- All medical device reports and information submitted to manufacturers and/or the FDA;

- Any information that was evaluated for the purpose of preparing the submission of annual reports; and

- Systems that ensure access to information for facilitating timely follow-up and inspection by the FDA.

4. Corrective and Preventive Actions are Inadequately Documented

Under 21 CFR 820.100(b), manufacturers of medical devices must document all activities and results of activities related to corrective/ preventive action procedures. In other words, the FDA wants solid proof of a fully functional CAPA system that includes:

- A documented analysis of the sources of quality data (for example, incoming raw materials, manufacturing processes, inventory management, etc.);

- Documentation of investigations of the causes of nonconformities;

- Documentation of the actions needed to correct and prevent the recurrence of nonconforming products or other quality problems;

- Documentation of the procedures used to verify or validate corrective actions;

- Documentation of the procedures used in the implementation of corrective and preventative actions;

- Documentation that demonstrates that information about nonconforming products or quality problems is being properly disseminated to the responsible parties; and

- Documentation that demonstrates that information about nonconforming products (or quality problems) is being properly disseminated for management review.

5. Process Validation Procedures are Inadequate

Under 21 CFR 820.75(a), where the results of a process cannot be fully verified by subsequent inspection and testing, the process must be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and, where appropriate, the major equipment validated, must be documented.

6. Quality Audits were not Adequately Conducted

Section 21 CFR 820.22 states that quality audits must be conducted by individuals who do not have direct responsibility for the matters being audited, and corrective action(s), including a re-audit of deficient matters, must be taken when necessary. A report of the results of each quality audit, and re-audit(s) where taken, must be made and such reports must be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and re-audits must be documented.

Hence, the sixth most common reason for getting an Obs. 483 or Warning Letter is because the FDA believes that a quality audit may not have been conducted properly, for one (or more) of the following reasons:

- The quality audit was not conducted by the proper individuals;

- Necessary corrective actions (including re-audits) were not taken;

- A report of the results of the quality audit (and any necessary re-audits) were not made according to FDA specifications; and/or

- The quality audit (or re-audit) report was not reviewed by management having responsibility for the matters audited.

7. Executive Management Failed to Ensure Quality at all Organizational Levels

Under 21 CFR 820.20, management with executive responsibility must ensure an adequate and effective quality system at all levels of the organization.

- **Quality Policy:** Management with executive responsibility must establish its policy and objectives for, and commitment to, quality. Management with executive responsibility must also ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

- **Organization:** Each manufacturer must establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements listed below:

    - **Responsibility and authority:** Each manufacturer must establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality; in addition, each manufacturer must provide the independence and authority necessary to perform these tasks.

    - **Resources:** Each manufacturer must provide adequate resources, including the assignment of trained personnel, for the management and performance of work, and for assessment activities, including internal quality audits.

    - **Management representative:** Management with executive responsibility must appoint and document the appointment of a member of management who, irrespective of other responsibilities, must have established authority over and responsibility for (i) ensuring that quality system requirements are effectively established and effectively maintained in accordance with the stipulations defined in this section, and (ii) reporting on the performance of the quality system to management with executive responsibility for review.

- **Management review:** Management with executive responsibility must review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews must be documented.

- **Quality planning:** Each manufacturer must establish a quality plan which defines the quality practices, resources, and activities relevant to devices that are designed and manufactured. The manufacturer must establish how the requirements for quality will be met.

- **Quality system procedures:** Each manufacturer must establish quality system procedures and instructions. An outline of the structure of the documentation used in the quality system must be established where appropriate.

8. Procedures for Conducting Quality Audits are Inadequate

Under 21 CFR 820.22, manufacturers of medical devices must establish procedures for quality audits and conduct such audits to assure that their quality system is in compliance with their established quality system requirements, and to determine the effectiveness of their established quality system.

Hence, the eighth most common reason for getting an Obs. 483 or Warning Letter has to do with the manufacturer's procedures for conducting a quality audit. If the FDA believes that the procedures are inadequate, the reason may be because:

- The manufacturer doesn't have procedures for conducting quality audits;

- The manufacturer has procedures for conducting quality audits, but the procedures are not in compliance with the manufacturer's established quality system requirements; or

- The manufacturer has procedures that are in compliance with the manufacturer's established quality system requirements, but the system requirements are not adequate for determining the effectiveness of the established quality system.

9. Procedures for Controlling the Design Process are Inadequate

Section 820.30(a) stipulates that each manufacturer of any class II or class III device, and the class I devices listed in below, must establish and maintain procedures for controlling the design of the device in order to ensure that specified design requirements are met.

Class I devices that are subject to design controls include:

(i) Devices automated with computer software; and

(ii) The devices listed in the following table:

Section	Device
868.6810	Catheter, Tracheobronchial Suction
878.4460	Glove, Surgeon's
880.6760	Restraint, Protective
892.5650	System, Applicator, Radionuclide, Manual
892.5740	Source, Radionuclide Teletherapy

10. Procedures for Design Changes are Inadequate or weren't followed during the Design Change Validation/ Verification Process

Section 820.30(i) stipulates that each manufacturer must establish and maintain procedures for identifying, documenting, validating (or, where appropriate, verifying), reviewing, and approving design changes before their implementation.

The MasterControl™ Solution

MasterControl™ GxP process management software consists of configurable, easy-to-use, connected applications for automating, streamlining, and effectively managing document control, change control, training control, audits, corrective/preventive action (CAPA), customer complaints, and other documents- and forms-based quality and business processes under a single, web-based platform. Hundreds of companies use MasterControl to meet stringent FDA regulations and many others also use it to comply with ISO quality standards and Sarbanes-Oxley Act requirements.

Here's how MasterControl helps avoid FDA 483 Obs. and Warning Letters:

Reason for Obs. 483 or Warning Letter	How MasterControl can Help
#1 Complaint Handling Procedures are Inadequate 21 CFR 820.198(a)	MasterControl Customer Complaints™ provides a simple, three-step process via a preconfigured, multi-page form for automating all tasks pertaining to customer complaints including: • Proper logging of complaints; • Capture of complete information from across the enterprise, regardless of who gets the complaint; • Data collection, notification, follow-up, and escalation; • Timely investigation; coordinated resolution; and • Shorter complaint (submission-to-resolution) lifecycle. Every step of the process is documented to ensure that all complaints, regardless of where they come from—e-mail, phone, fax, letters, corporate web site, sales reps, etc.—are properly logged, investigated, reported to the FDA (if warranted), and resolved in a timely manner.
#2 Corrective and Preventive Action (CAPA Procedures) are Inadequate 21 CFR 820.100(a)	MasterControl CAPA™ automates all CAPA tasks, including routing, notification, follow-up, escalation, and approval of CAPAs and related documents. MasterControl CAPA is based on a team-oriented, problem-solving procedure involving an 8-step process (see description of 8-step process after this table).

#3 Written Medical Device Reporting (MDR) Procedures are Inadequate 21 CFR 803.17	Medical device reporting (MDR) is the mechanism by which the FDA receives information about significant medical device adverse events. In its warning letters, FDA frequently cites a company's lack of a formal process for reviewing, evaluating, and investigating complaints, and reporting the serious cases to the agency via the MDR system. Thus, MDR deficiencies usually stem from improper complaint handling and reporting. As part of its customer complaints handling solution, MasterControl provides a pre-configured, multi-page electronic form that ensures the accurate capture of all relevant information from customer complaints. The solution includes the FDA's MedWatch 3500A form for mandatory reporting of adverse events to ensure that all required data are immediately collected and handed over to an adverse events specialist.
#4 Corrective and Preventive Action (CAPA) Procedures have not been Adequately Documented FDA regulation 21 CFR 820.100(b)	MasterControl CAPA tracks all routing information and data entered into the electronic CAPA form and stores this information in a centralized repository that makes search and retrieval easy during inspections and audits.
#5 Process Validation Procedures are Inadequate FDA regulation 21 CFR 820.75(a)	MasterControl supports process validation activities through its project and document management software. Designed to coordinate and track the rigorous validation testing, data analysis, and documentation requirements involved in developing a quality product for regulatory approval, MasterControl Projects™ connects the project plan to assigned tasks and provides automatic updates as soon as tasks are completed. Automating scheduling, task assignment, routing, tracking, escalation, and approval help ensure efficiency and quality, and greatly accelerate the validation process. Integrated document control capabilities make it easy to collaborate on, approve, and access protocols, reports, and test data.

#6 Quality Audits are not Adequately Conducted FDA regulation 21 CFR 820.22	To help ensure compliance, MasterControl Audit™ automates, streamlines, and effectively manages the audit process. The solution provides advanced tracking capabilities—from scheduling and planning through execution and completion—in addition to best practice forms for recording basic audit information and audit findings. MasterControl Audit automates the scheduling of all recurring audit-related activities and provides analytics and reporting capabilities for increased management visibility. (Please see Item #8 in this table for more information.)
#7 Executive Management Failed to Ensure Quality at all Organizational Levels FDA regulation 21 CFR 820.20	To help management ensure quality at all organizational levels, the MasterControl™ GxP Process Management Software suite provides configurable, easy-to-use, and connected solutions for automating, streamlining, and effectively managing document control, change control, training, audits, nonconformances, corrective/preventive action (CAPA), customer complaints, and other documents- and forms-based quality and business processes. MasterControl's centralized document repository and web-based platform provide authorized users with access to up-to-date documents in the DHF, DHR, and DMR. In addition, system transparency and the system's ability to generate customizable reports that provide the real-time status of the entire quality system keep members of the management team well informed, so that they can ensure quality at all organizational levels.

#8 Procedures for Conducting Quality Audits are Inadequate FDA regulation 21 CFR 820.22	A quality audit in a regulated company is the equivalent of a medical examination of a patient. It is a necessary procedure for evaluating a quality system's general "health" and for "diagnosing" problems in order to correct them. MasterControl Audit™ automates all procedures pertaining to the audit process via two important best practice forms for collecting and tracking data: • **Audit Summary form**, which tracks basic information about an audit (type of audit, audit date, description, objective, and scope, audit area and lead auditor); this form also serves as a tool for gathering information, such as the regulation or procedure that is the basis for the audit, the audit agenda, audit team members, and checklists. • **Audit Finding form**, which tracks findings resulting from the audit and helps evaluate risk, based on the category and severity of risk and the likelihood of recurrence; this form also specifies whether a CAPA is required and provides proper closure by tracking verification of the process owner's response to the finding. MasterControl Audit includes notification, follow-up, and escalation of overdue assignments to ensure that quality audits are completed on schedule.
#9 Procedures for Controlling the Design Process are Inadequate 21 CRF 820.30(a)	MasterControl provides secure, centralized virtual vaults for the management of design control documents. Unreleased design documents can be locked to prevent multiple users from simultaneously changing the design. DIR, FMEA, test protocols and reports, as well as specifications and other documents created or reviewed during the product definition phase, reside in the "draft" vault while being worked on, and, when approved, automatically move to the "approved/ released" vault. This makes it easy for authorized users to locate the most recent version of design documents, and it prevents unauthorized design control documents from being accidentally released. Automatic archiving and cataloguing of "outdated" documents provides a GxP-compliant audit trail.

#10 Procedures for Design Changes are Inadequate or weren't followed during the Design Change Validation/ Verification Process 21 CRF 820.30(i)	MasterControl Change Control™ helps ensure that procedures for design changes are both adequate and followed during the design change verification/validation process by providing a pre-configured, multi-page, best-practice, electronic form for collecting and tracking data throughout the entire change process. The form captures information such as description of change, justification, and impact. An initiator can use a single form for initiating multiple changes (for example, changes in a component and in ten products the component is used in). This assures the adequacy of the design change procedures by making sure that changes are immediately implemented in all affected components and devices. The form also incorporates priority level and prompts the user to make a risk assessment of the change (low, medium, or high). Any high-level change implies great impact on the product and is likely to require a regulatory filing. Customizable reports provide the real-time status not only of change control tasks but of the entire quality system.

Eight Step CAPA Procedure	
Step 1	Form an appropriate cross-functional team. The team should include a champion who has the resources and authority to implement the team's solution.
Step 2	Define the problem.
Step 3	Contain the problem. Protect the customer from the problem. This step can be omitted when 8D is used for a proactive improvement because there is no "problem" (like defective parts).
Step 4	Identify the root cause.
Step 5	Select a permanent correction.
Step 6	Implement the corrective action and verify its effectiveness.
Step 7	Make the change permanent (standardization). Also share the solution with similar operations. This is best practice deployment.
Step 8	Recognize the team's achievement.

Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

Procedural
October 2009

Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
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Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
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http://www.fda.gov/cber/guidelines.htm.
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U.S. Department of Health and Human Services
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Center for Devices and Radiological Health (CDRH)

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I. INTRODUCTION

This guidance provides an overview of the responsibilities of a person who conducts a clinical investigation of a drug, biological product, or medical device (an *investigator* as defined in 21 CFR 312.3(b) and 21 CFR 812.3(i)). The goal of this guidance is to help investigators better meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations. This guidance is intended to clarify for investigators and sponsors FDA's expectations concerning the investigator's responsibility (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and (2) to protect the rights, safety, and welfare of study subjects.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. OVERVIEW OF INVESTIGATOR RESPONSIBILITIES

In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible for:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

[1] This guidance has been prepared by the Investigator Responsibilities Working Group, which includes representatives from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

Although specific investigator responsibilities in drug and biologics clinical trials are not identical to the investigator responsibilities in medical device clinical trials, the general responsibilities are essentially the same. This guidance discusses the general investigator responsibilities that are applicable to clinical trials of drugs, biologics, and medical devices.

An investigator's responsibilities in conducting clinical investigations of ***drugs*** or ***biologics*** are provided in 21 CFR Part 312. Many of these responsibilities are included in the required investigator's signed statement, Form FDA-1572 (see Attachment A) (hereinafter referred to as 1572). Note that although the 1572 specifically incorporates most of the requirements directed at investigators in part 312, not all requirements are listed in the 1572. Investigators and sponsors should refer to 21 CFR Parts 11, 50, 54, 56, and 312 for a more comprehensive listing of FDA's requirements for the conduct of drug and biologics studies.[2]

An investigator's responsibilities in conducting clinical investigations of a ***medical device*** are provided in 21 CFR Part 812, including the requirement that there be a signed agreement between the investigator and sponsor (see 21 CFR 812.43(c)(4) and 812.100). The medical device regulations do not require use of a specific form for an investigator's statement; and there are additional requirements not listed above (see Attachment B). Investigators and sponsors should refer to 21 CFR Parts 11, 50, 54, 56, and 812 for a more comprehensive listing of FDA's requirements for the conduct of device studies.

Nothing in this guidance is intended to conflict with recommendations for investigators contained in the International Conference on Harmonisation (ICH) guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance* (Good Clinical Practice Guidance).[3]

III. CLARIFICATION OF CERTAIN INVESTIGATOR RESPONSIBILITIES

This section of the guidance clarifies the investigator's responsibility to supervise the conduct of the clinical investigation and to protect the rights, safety, and welfare of participants in drug and medical device clinical trials.

A. Supervision of the Conduct of a Clinical Investigation

As stated above, investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312, commit themselves to personally conduct or supervise the investigation. Investigators who conduct clinical investigations of medical devices, under 21 CFR Part 812, commit themselves to supervise all testing of the device involving human subjects. It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

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[2] As a reminder, some investigators may be responsible for submitting certain clinical trial information to the National Institutes of Health clinical trials data bank under 42 U.S.C 282(j), 402(j) of the Public Health Service Act. Although not all investigators will be expected to meet this requirement, go to www.clinicaltrials.gov for further information about potential responsibilities.

[3] Guidances, including ICH guidances, are available on the Agency's Web page. See the Web addresses on the second title page of this guidance.

In assessing the adequacy of supervision by an investigator, FDA focuses on four major areas: (1) whether individuals who were delegated tasks were qualified to perform such tasks, (2) whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study, (3) whether there was adequate supervision and involvement in the ongoing conduct of the study, and (4) whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

1. What Is Appropriate Delegation of Study-Related Tasks?

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task. Appropriate delegation is primarily an issue for tasks considered to be clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing medical care to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Licensing requirements may vary by jurisdiction (e.g., states, countries). Investigators should take such qualifications/licensing requirements into account when considering delegation of specific tasks. In all cases, a qualified physician (or dentist) should be responsible for all trial-related medical (or dental) decisions and care.[4]

During inspections of investigation sites, FDA has identified instances in which study tasks have been delegated to individuals lacking appropriate qualifications. Examples of tasks that have been inappropriately delegated include:

- Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria
- Physical examinations
- Evaluation of adverse events
- Assessments of primary study endpoints
- Obtaining informed consent

The investigator is responsible for conducting studies in accordance with the protocol (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). In some cases a protocol may specify the qualifications of the individuals who are to perform certain protocol-required tasks (e.g., physician, registered nurse), in which case the protocol must be followed even if state law permits individuals with different qualifications to perform the task (see 21 CFR 312.23(a)(6) and 312.40(a)(1)). For example, if the state in which the study site is located permits a nurse practitioner or physician's assistant to perform physical examinations under the supervision of a physician, but the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated.[5] This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks

[4] Guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance*, section 4.3.1.
[5] Ibid, section 4.1.5

(e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

2. What Is Adequate Training?

The investigator should ensure that there is adequate training for all staff participating in the conduct of the study, including any new staff hired after the study has begun to meet unanticipated workload or to replace staff who have left. The investigator should ensure that staff:

- Are familiar with the purpose of the study and the protocol
- Have an adequate understanding of the specific details of the protocol and attributes of the investigational product needed to perform their assigned tasks
- Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials and the protection of human subjects
- Are competent to perform or have been trained to perform the tasks they are delegated
- Are informed of any pertinent changes during the conduct of the trial and receive additional training as appropriate

If the sponsor provides training for investigators in the conduct of the study, the investigator should ensure that staff receive the sponsor's training, or any information (e.g., training materials) from that training that is pertinent to the staff's role in the study.

3. What Is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?

For each study site, there should be a distinct individual identified as an investigator who has supervisory responsibility for the site. Where there is a subinvestigator at a site, that individual should report directly to the investigator for the site (i.e., the investigator should have clear responsibility for evaluating the subinvestigator's performance and the authority to terminate the subinvestigator's involvement with the study) and the subinvestigator should not be delegated the primary supervisory responsibility for the site.

The investigator should have sufficient time to properly conduct and supervise the clinical trial. The level of supervision should be appropriate to the staff, the nature of the trial, and the subject population. In FDA's experience, the following factors may affect the ability of an investigator to provide adequate supervision of the conduct of an ongoing clinical trial at the investigator's site:

- Inexperienced study staff
- Demanding workload for study staff
- Complex clinical trials (e.g., many observations, large amounts of data collected)
- Large number of subjects enrolled at a site
- A subject population that is seriously ill
- Conducting multiple studies concurrently
- Conducting a study from a remote (e.g., off-site) location
- Conducting a study at multiple sites under the oversight of a single investigator, particularly where those sites are not in close proximity

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified

and experienced. A plan might include the following elements, to the extent they apply to a particular trial:

- Routine meetings with staff to review trial progress, adverse events, and update staff on any changes to the protocol or other procedures
- Routine meetings with the sponsor's monitors
- A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
- A procedure for documenting or reviewing the performance of delegated tasks in a satisfactory and timely manner (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
- A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation and the risks
- A procedure for ensuring that source data are accurate, contemporaneous, and original
- A procedure for ensuring that information in source documents is accurately captured on the case report forms (CRFs)
- A procedure for dealing with data queries and discrepancies identified by the study monitor
- Procedures for ensuring study staff comply with the protocol and adverse event assessment and reporting requirements
- A procedure for addressing medical and ethical issues that arise during the course of the study in a timely manner

4. What Are an Investigator's Responsibilities for Oversight of Other Parties Involved in the Conduct of a Clinical Trial?

a. Study Staff Not in the Direct Employ of the Investigator

Staff involved directly in the conduct of a clinical investigation may include individuals who are not in the direct employ of the investigator. For example, a site management organization (SMO) may hire an investigator to conduct a study and provide the investigator with a study coordinator or nursing staff employed by the SMO. In this situation, the investigator should take steps to ensure that the staff not under his/her direct employ are qualified to perform delegated tasks (see section III.A.1) and have received adequate training on carrying out the delegated tasks and on the nature of the study (see section III.A.2), or the investigator should provide such training. The investigator should be particularly cautious where documentation needed to comply with the investigator's regulatory responsibilities is developed and maintained by SMO staff (e.g., source documents, CRFs, drug storage and accountability records, institutional review board correspondence). A sponsor who retains an SMO shares responsibility for the quality of the work performed by the SMO.

The investigator is responsible for supervising the study tasks performed by this staff, even though they are not in his/her direct employ during the conduct of the study (see section III.A.3). This responsibility exists regardless of the qualifications and experience of staff members. In the event that the staff's performance of study-related tasks is not adequate

and cannot be made satisfactory by the investigator, the investigator should document the observed deficiencies in writing to the staff member's supervisor(s) and inform the sponsor. Depending on the severity of the deficiencies, the clinical trial may need to be voluntarily suspended until personnel can be replaced.

b. Parties Other than Study Staff

There are often critical aspects of a study performed by parties not involved directly in patient care or contact and not under the direct control of the clinical investigator. For example, clinical chemistry testing, radiologic assessments, and electrocardiograms are commonly done by a central independent facility retained by the sponsor. Under these arrangements, the central facility usually provides the test results directly to the sponsor and to the investigator. Because the activities of these parties are critical to the outcome of the study and because the sponsor retains the services of the facility, the sponsor is responsible for ensuring that these parties are competent to fulfill and are fulfilling their responsibilities to the study.

Less frequently, a study may require that investigators arrange to obtain information critical to the study that cannot be obtained at the investigator's site. For example, if the study protocol requires testing with special equipment or expertise not available at the investigator's site, the investigator might make arrangements for an outside facility to perform the test. In this case, the results are usually provided directly to the investigator, who then submits the information to the sponsor. If the investigator retains the services of a facility to perform study assessments, the investigator should take steps to ensure that the facility is adequate (e.g., has the required certification or licenses). The investigator may also institute procedures to ensure the integrity of data and records obtained from the facility providing the information (e.g., a process to ensure that records identified as coming from the facility are authentic and accurate). Procedures are particularly important when assessments are crucial to the evaluation of the efficacy or safety of an intervention or to the decision to include or exclude subjects who would be exposed to unreasonable risk.

Investigators should carefully review the reports from these external sources for results that are inconsistent with clinical presentation. To the extent feasible, and considering the specifics of study design, investigators should evaluate whether results appear reasonable, individually, and in aggregate, and they should document the evaluation. If investigators detect possible errors or suspect that results from a central laboratory or testing facility might be questionable, the investigator should contact the sponsor immediately.

c. Special Considerations for Medical Device Studies

Field clinical engineers (device sponsor employees) have traditionally played a role in some investigational device procedures (e.g., cardiology, orthopedics, and ophthalmology) by providing technical assistance to the device investigator. The field clinical engineer should be supervised by the investigator because the field clinical engineer's presence or activities may have the potential to bias the outcome of studies, may affect the quality of research data, and/or may compromise the rights and welfare of human subjects. The field clinical engineer's activities should be described in the protocol. If the field engineer has

face-to-face contact with subjects or if the activities of the field engineer directly affect the subject, those activities should also be described in the informed consent.

B. Protecting the Rights, Safety, and Welfare of Study Subjects

Investigators are responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial (21 CFR 312.60 and 812.100). This responsibility should include:

- Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
- Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
- Adhering to the protocol so that study subjects are not exposed to unreasonable risks

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.

1. Reasonable Medical Care Necessitated by Participation in a Clinical Trial

During a subject's participation in a trial, the investigator (or designated subinvestigator) should ensure that reasonable medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial participation. If the investigator does not possess the expertise necessary to provide the type of medical care needed by a subject, the investigator should make sure that the subject is able to obtain the necessary care from a qualified practitioner. For example, if the study involves placement of a carotid stent by an interventional neuroradiologist and the subject suffers a cerebral stroke, the neuroradiologist should assess the clinical status of the subject and arrange for further care of the subject by a neurologist. Subjects should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention that develops during or after the course of their participation in a study, even if the follow-up period extends beyond the end of the study at the investigative site.

The investigator should also inform a subject when medical care is needed for conditions or illnesses unrelated to the study intervention or the disease or condition under study when such condition or illness is readily apparent or identified through the screening procedures and eligibility criteria for the study. For example, if the investigator determines that the subject has had an exacerbation of an existing condition unrelated to the investigational product or the disease or condition under study, the investigator should inform the subject. The subject should also be advised to seek appropriate care from the physician who was treating the illness prior to the study, if there is one, or assist the subject in obtaining needed medical care.

2. Reasonable Access to Medical Care

Investigators should be available to subjects during the conduct of the trial for medical care related to participation in the study. Availability is particularly important when subjects are receiving a drug that has significant toxicity or abuse potential. For example, if a study drug has potentially fatal toxicity, the investigator should be readily available by phone or other electronic communication 24 hours a day and in reasonably close proximity to study subjects (e.g., not in

another state or on prolonged travel). Study subjects should be clearly educated on the possible need for such contact and on precisely how to obtain it, generally by providing pertinent phone numbers, e-mail addresses, and other contact information, in writing. Prior to undertaking the conduct of a study, prospective investigators should consider whether they can be available to the extent needed given the nature of the trial.

During any period of unavailability, the investigator should delegate responsibility for medical care of study subjects to a specific qualified physician who will be readily available to subjects during that time (in the manner a physician would delegate responsibility for care in clinical practice). If the investigator is a non-physician, the investigator should make adequate provision for any necessary medical care that the investigator is not qualified to provide.

3. Protocol Violations that Present Unreasonable Risks

There are occasions when a failure to comply with the protocol may be considered a failure to protect the rights, safety, and welfare of subjects because the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks (e.g., enrolling a subject with decreased renal function in a trial in which decreased function is exclusionary because the drug may be nephrotoxic) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Similarly, failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that causes neutropenia) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Investigators should seek to minimize such risks by adhering closely to the study protocol.

ATTACHMENT A: COPY OF FORM 1572

DEPARTMENT OF HEALTH AND HUMAN SERVICES **FOOD AND DRUG ADMINISTRATION** **STATEMENT OF INVESTIGATOR** ***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*** (See instructions on reverse side.)	Form Approved: OMB No. 0910-0014. Expiration Date: May 31, 2009. *See OMB Statement on Reverse.* **NOTE:** No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

ATTACHMENT B: INVESTIGATOR RESPONSIBILITIES

FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS

This document is intended to assist investigators in identifying and complying with their responsibilities in connection with the conduct of clinical investigations involving medical devices. Although this guidance primarily addresses duties imposed upon clinical investigators by regulations of the Food and Drug Administration (FDA), investigators should be cognizant of additional responsibilities that may derive from other sources (such as the study protocol itself, the investigator agreement, any conditions of approval imposed by FDA or the governing institutional review board, as well as institutional policy and state law).

GENERAL RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.100)

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations

2. Protecting the rights, safety, and welfare of subjects under the investigator's care

3. Controlling devices under investigation

4. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50 and that the study is not commenced until FDA and IRB approvals have been obtained.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.110)

1. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation

2. Conducting the investigation in accordance with:
    a. The signed agreement with the sponsor
    b. The investigational plan
    c. The regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations
    d. Any conditions of approval imposed by an IRB or FDA

3. Supervising the use of the investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it.

4. Disposing of the device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

MAINTAINING RECORDS (21 CFR 812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA

2. Records of receipt, use or disposition of a device that relate to:
   a. The type and quantity of the device, dates of receipt, and batch numbers or code marks
   b. Names of all persons who received, used, or disposed of each device
   c. The number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore

3. Records of each subject's case history and exposure to the device, including:
   a. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent
   b. All relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests;
   c. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol

5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation

INSPECTIONS (21 CFR 812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.

SUBMITTING REPORTS (21 CFR 812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. To the sponsor and the IRB:
   - Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)
   - *Progress reports* on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)
   - Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)
   - Any use of the device *without obtaining informed consent*. (Due within 5 working days after such use.)
   - A *final report.* (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")
   - *Any further information* requested by FDA or the IRB about any aspect of the investigation.

2. To the Sponsor:
   - *Withdrawal of IRB approval* of the investigator's part of an investigation. (Due within 5 working days of such action).

INVESTIGATIONAL DEVICE DISTRIBUTION AND TRACKING

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it (21 CFR 812.110(c)). The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of devices. Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (21 CFR 812.110(e)). Investigators must also maintain complete, current, and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140(a)(2)). Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

PROHIBITION OF PROMOTION AND OTHER PRACTICES (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator) and encompasses the following activities:

1. Promotion or test marketing of the investigational device

2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling

3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective

4. Representing that the device is safe or effective for the purposes for which it is being investigated

HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP)

GUIDANCE FOR IMPLEMENTATION

World Health Organization

WHO Library Cataloguing-in-Publication Data

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Guidance for implementation

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Preamble

Clinical research is necessary to establish the safety and effectiveness of specific health and medical products and practices. Much of what is known today about the safety and efficacy of specific products and treatments has come from randomized controlled clinical trials[1] that are designed to answer important scientific and health care questions. Randomized controlled trials form the foundation for "evidence-based medicine", but such research can be relied upon only if it is conducted according to principles and standards collectively referred to as "Good Clinical Research Practice" (GCP).

This handbook is issued as an adjunct to WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products" (1995), and is intended to assist national regulatory authorities, sponsors, investigators and ethics committees in implementing GCP for industry-sponsored, government-sponsored, institution-sponsored, or investigator-initiated clinical research. The handbook is based on major international guidelines, including GCP guidelines issued subsequent to 1995, such as the International Conference on Harmonization (ICH) Good Clinical Practice: Consolidated Guideline and is organized as a reference and educational tool to facilitate understanding and implementation of GCP by:

- describing the clinical research process as it relates to health and medical products, and identifying and explaining each of the activities that are common to most trials and the parties who are ordinarily responsible for carrying them out;
- linking each of these processes to one or more Principle(s) of GCP within this Handbook;

[1] These trials assign trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

- explaining each GCP Principle and providing guidance on how each Principle is routinely applied and implemented;
- directing the reader to specific international guidelines or other references that provide more detailed advice on how to comply with GCP.

Introduction

Good Clinical Research Practice (GCP) is a process that incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects. Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines, and ensures the integrity of clinical research data. The conduct of clinical research is complex and this complexity is compounded by the need to involve a number of different individuals with a variety of expertise, all of who must perform their tasks skillfully and efficiently.

The responsibility for GCP is shared by all of the parties involved, including sponsors, investigators and site staff, contract research organizations (CROs), ethics committees, regulatory authorities and research subjects.

Background

For the purposes of this handbook, a general definition of human research is:

> "Any proposal relating to human subjects including healthy volunteers that cannot be considered as an element of accepted clinical management or public health practice and that involves either (i) physical or psychological intervention or observation, or (ii) collection, storage and dissemination of information relating to individuals. This definition relates not only to planned trials involving human subjects but to research in which environmental factors are manipulated in a way that could incidentally expose individuals

to undue risks." (World Health Organization, *Governance, rules and procedures*, WHO Manual XVII).

Before medical products can be introduced onto the market or into public health programmes, they must undergo a series of investigations designed to evaluate safety and efficacy within the parameters of toxicity, potency, dose finding, and field conditions. Full information must be documented on therapeutic indications, method of administration and dosage, contraindications, warnings, safety measures, precautions, interactions, effects in target populations and safety information.

During the clinical research and development process, most medical products will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. In some cases, as few as 100, and rarely more than 5000 subjects will have received the product prior to its approval for marketing. Given these circumstances and because the decision to allow a new product on the market has such broad public health significance, the clinical trial process and data must conform to rigorous standards to ensure that decisions are based on data of the highest quality and integrity.

In the early 1960s, widespread concern about the safety and control of investigational drugs and the clinical research process developed among members of the medical profession, the scientific community, regulatory authorities, and the general public. In 1968, WHO convened a Scientific Group on Principles for Clinical Evaluation of Drugs. The Scientific Group was charged with reviewing and formulating principles for clinical evaluation of drug products, whether new or already marketed, including considerations for new indications or dosage forms for marketed products and new combination products. In 1975, another WHO Scientific Group was convened to specifically consider all aspects of the evaluation and testing of drugs and to formulate proposals and guidelines for research in the field of drug development. These reports formed the basis for WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products", published in 1995, as well as many national and international guidelines that have subsequently been developed, including:

- International Conference on Harmonization (ICH) E6, "Good Clinical Practice: Consolidated Guideline" (1996)
- International Standards Organization (ISO), "Clinical investigation of medical devices for human subjects, Part I (General requirements) and Part 2 (Clinical investigation plans) (2001)
- Pan American Health Organization (PAHO). Pan American Network on Drug Regulatory Harmonization (PANDRH). "Good Clinical Practices: Document of the Americas" (2005)

The conduct of clinical research in accordance with the principles of GCP helps to ensure that clinical research participants are not exposed to undue risk, and that data generated from the research are valid and accurate. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, GCP not only serves the interests of the parties actively involved in the research process, but also protects the rights, safety and well-being of subjects and ensures that investigations are scientifically sound and advance public health goals.

Objectives of this handbook

The objectives of this current WHO Handbook for GCP include the following:

- To support and promote the achievement of a globally applicable unified standard for the conduct of **all** clinical research studies on human subjects;
- To provide an overview and practical advice on the application and implementation of internationally accepted principles for GCP and clinical research in human subjects;
- To provide an educational and reference tool for anyone interested in, or intending to become or already actively engaged in, clinical research by providing the necessary background and insight into the reasons for the requirements of GCP and their efficient application;

- To assist editors in evaluating the acceptability of reported research for publication, and regulators in evaluating the acceptability of any study that could affect the use or the terms of registration of a medical product.

This handbook can be adopted or referenced by WHO Member States. Where national regulations or requirements do not exist or require supplementation, relevant regulatory authorities may designate or adopt these GCP principles and standards. Where national or adopted international standards are more demanding than WHO GCP, the former should take precedence.

Guidance on various aspects of clinical research is also available from several other national and international bodies such as, the International Conference on Harmonization (ICH), the International Standards Organization (ISO), and the Council for International Organizations of Medical Sciences (CIOMS), the European Agency for the Evaluation of Medicinal Products (EMEA), and the United States Food and Drug Administration (FDA). (See References)

Scope of this handbook

This handbook defines fourteen principles of GCP, and provides guidance and assistance in the application and implementation of these principles by all parties involved in the clinical research process. In describing each principle, the handbook articulates the research processes and systems that need to be in place, and within these, the roles and responsibilities of various stakeholders (notably sponsors, investigators, ethics committees, and regulatory authorities) involved in the conduct of health and clinical research studies.

To the extent possible, the principles of GCP should generally apply to all clinical research involving human subjects, and not just research involving pharmaceutical or other medical products. Included here are:

- studies of a physiological, biochemical, or pathological process, or of the response to a specific intervention – whether physical, chemical, or psychological – in healthy subjects or in patients;

- controlled studies of diagnostic, preventive or therapeutic measures, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;
- studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures;
- studies concerning human health-related behaviour in a variety of circumstances and environments;
- studies that employ either observation or physical, chemical, or psychological intervention. Such studies may generate records or make use of existing records containing biomedical or other information about individuals who may or may not be identifiable from the records or information. The use of such records and the protection of the confidentiality of data obtained from those records are discussed in the "International Guidelines for Ethical Review of Epidemiological Studies" (CIOMS, 1991, currently being updated).

Although some principles of GCP may not apply to all types of research on human subjects, consideration of these principles is strongly encouraged wherever applicable as a means of ensuring the ethical, methodologically sound and accurate conduct of human subject's research.

Overview of the clinical research process

This section outlines key activities involved in the conduct of a clinical trial. This shows one possible sequence in which these activities may occur; other sequences (e.g., simultaneous completion of one or more activities) are also acceptable. Multiple parties are responsible for the success of these activities and procedures; the individual responsibilities of investigators, sponsors, ethics committees, and regulatory authorities will be the topic of subsequent sections of this Handbook.

Key trial activities include:

1. Development of the trial protocol

Within GCP, clinical trials should be described in a clear, detailed protocol.

The sponsor, often in consultation with one or more clinical investigators, generally designs the study protocol; clinical investigators may also design and initiate clinical studies, as sponsor-investigators. Integral to protocol development are the concepts of risk identification, study design and control groups, and statistical methodology. The sponsor and clinical investigator(s) should be aware of any national/local laws or regulations pertaining to designing, initiating, and conducting the study.

See WHO GCP Principles 2: Protocol; 3: Risk Identification; 4: Benefit-Risk Assessment.

2. Development of standard operating procedures (SOPs)

All parties who oversee, conduct or support clinical research (i.e., sponsors, clinical investigators, Independent Ethics Committees/

Institutional Review Boards [IECs/IRBs] monitors, contract research organizations [CROs]) should develop and follow written standard operating procedures (SOPs) that define responsibilities, records, and methods to be used for study-related activities.

See WHO GCP Principles 6: Protocol Compliance; 7: Informed Consent; 11: Records; 12: Confidentiality/Privacy; and 14: Quality Systems.

Sponsors should consider preparing SOPs for

- developing and updating the protocol, investigator's brochure, case report forms (CRFs), and other study-related documents;
- shipping, handling, and accounting for all supplies of the investigational product;
- standardizing the activities of sponsors and study personnel (e.g., review of adverse event reports by medical experts; data analysis by statisticians);
- standardizing the activities of clinical investigators to ensure that trial data is accurately captured;
- monitoring, to ensure that processes are consistently followed and activities are consistently documented;
- auditing, to determine whether monitoring is being appropriately carried out and the systems for quality control are operational and effective.

Similarly, clinical investigators should consider developing SOPs for common trial-related procedures not addressed in the protocol. These may include but are not limited to: communicating with the IEC/IRB; obtaining and updating informed consent; reporting adverse events; preparing and maintaining adequate records; administering the investigational product; and accounting for and disposing of the investigational product.

IECs/IRBs should develop and follow written procedures for their operations, including but not limited to: membership requirements; initial and continuing review; communicating with the investigator(s) and institution; and minimizing or eliminating conflicts of interest.

Regulators should consider developing written procedures for activities pertaining to the regulation of clinical research. These may include but are not limited to: reviewing applications and safety reports; conducting GCP inspections (where applicable) and communicating findings to the inspected parties; and establishing an infrastructure for due process and imposing sanctions on parties who violate national/local law or regulations.

3. Development of support systems and tools

Appropriate support systems and tools facilitate the conduct of the study and collection of data required by the protocol. Support systems and tools include, but are not limited to, trial-related information documents (e.g., investigator's brochure, case report forms [CRFs], checklists, study flow sheets, drug accountability logs; see *Overview Process 4: Generation and approval of trial-related information documents*), computer hardware and software, electronic patient diaries, and other specialized equipment.

See WHO GCP Principles 2: Protocol; 11: Records; 14: Quality Systems.

The sponsor is generally responsible for developing, maintaining, modifying, and ensuring the availability of support systems and tools for conducting the trial and collecting and reporting required data.

For example, the sponsor may consider developing/designing/providing/designating:

- diagnostic or laboratory equipment required by the study protocol, and procedures/schedules for servicing the equipment according to the manufacturer's specifications;
- computer systems (hardware and software) to be used in the clinical trial (e.g., statistical or other software, electronic patient diaries, coding of personal data), and software validation systems, as needed;
- facsimile or other communications equipment to facilitate reporting of serious adverse events;
- information and training tools for clinical investigators and site personnel.

4. Generation and approval of trial-related documents

Development of trial-related documents may facilitate the conduct of the study, collection and reporting of study-related data, and analysis of study results.

The sponsor generally develops, designs, and provides various standardized forms and checklists to assist the clinical investigator and his/her staff in capturing and reporting data required by the protocol.

See WHO GCP Principles 2: Protocol; 7: Informed Consent; 11: Records; 14: Quality Systems.

Examples of trial information documents include, but are not limited to:

- investigator's brochure;
- checklists to identify and document the required steps for each of the various clinical trial activities (e.g., investigator selection, approvals and clearances, monitoring, adverse event reporting and evaluation, analysis of interim data);
- investigational supplies accountability forms to document the amount and source of investigational product shipped and received, the amount dispensed to subjects, and the return/destruction, as appropriate, of any unused product;
- signature logs and other forms to document by whom activities are completed, when, and the sequence in which they are carried out;
- case report forms (CRFs) for each scheduled study visit to capture all of the necessary data collected from and reported for each subject;
- informed consent documents;
- adverse event or safety reporting forms;
- administrative forms to track research funds and expenses;
- forms to disclose information about the investigator's financial, property, or other interests in the product under study, in accordance with national/local law or regulations;

- formats for reports of monitoring visits;
- formats for progress reports, annual reports, and final study reports.

5. Selection of trial sites and the selection of properly qualified, trained, and experienced investigators and study personnel

Clinical investigators must be qualified and have sufficient resources and appropriately trained staff to conduct the investigation and be knowledgeable of the national setting and circumstances of the site and study population(s). Sponsors should review the requirements of the study protocol to determine the type(s) of expertise required and identify clinical investigators who have the particular medical expertise necessary to conduct the study and who have knowledge, training and experience in the conduct of clinical trials and human subject protection.

See WHO GCP Principles 2: Protocol; 9: Investigator Qualifications; 10: Staff Qualifications.

6. Ethics committee review and approval of the protocol

Within GCP, studies must be reviewed and receive approval/favourable opinion from an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) prior to enrollment of study subjects.

The investigator generally assumes responsibility for obtaining IEC/IRB review of the study protocol. Copies of any approval/favourable opinion are then provided to the sponsor.

See WHO GCP Principles 1: Ethical Conduct; 2: Protocol; 4: Benefit-Risk Assessment; 5: Review by IEC/IRC; 7: Informed Consent; 8: Continuing Review/Ongoing Benefit-Risk Assessment; 11: Records; 12: Confidentiality/Privacy.

7. Review by regulatory authorities

Within GCP, studies must undergo review by regulatory authority(ies) for use of the investigational product or intervention in human subjects and to ensure that the study is appropriately designed to meet its stated objectives, according to national/regional/local law and regulations. [Note: Some countries may not have systems in place for reviewing research or may depend on external review. Also, some countries may have additional requirements for the review and approval of trial sites and/or investigators.]

The sponsor is generally responsible for ensuring that the applicable regulatory authority(ies) review and provide any required authorizations for the study before the study may proceed. The sponsor should also list the trial in applicable and/or required clinical trial registry(ies).

See WHO GCP Principles 2: Protocol; 4: Benefit-Risk Assessment.

8. Enrollment of subjects into the study: recruitment, eligibility, and informed consent

The clinical investigator has primary responsibility for recruiting subjects, ensuring that only eligible subjects are enrolled in the study, and obtaining and documenting the informed consent of each subject. Within GCP, informed consent must be obtained from each study subject prior to enrollment in the study or performing any specific study procedures.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 7: Informed Consent; 11: Records.

9. The investigational product(s): quality, handling and accounting

Quality of the investigational product is assured by compliance with Good Manufacturing Practices (GMPs) and by handling and storing the product according to the manufacturing specifications and the study protocol. GCP requires that sponsors control access to the in-

vestigational product and also document the quantity(ies) produced, to whom the product is shipped, and disposition (e.g., return or destruction) of any unused supplies. GCP also requires investigators to control receipt, administration, and disposition of the investigational product.

See WHO GCP Principles 2: Protocol; 11: Records; 13: Good Manufacturing Practice; 14: Quality Systems

10. Trial data acquisition: conducting the trial

Research should be conducted according to the approved protocol and applicable regulatory requirements. Study records documenting each trial-related activity provide critical verification that the study has been carried out in compliance with the protocol.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 11: Records.

11. Safety management and reporting

All clinical trials must be managed for safety. Although all parties who oversee or conduct clinical research have a role/responsibility for the safety of the study subjects, the clinical investigator has primary responsibility for alerting the sponsor and the IEC/IRB to adverse events, particularly serious/life-threatening unanticipated events, observed during the course of the research. The sponsor, in turn, has primary responsibility for reporting of study safety to regulatory authorities and other investigators and for the ongoing global safety assessment of the investigational product. A data and safety monitoring board (DSMB) may be constituted by the sponsor to assist in overall safety management.

See WHO GCP Principles 2: Protocol; 3: Risk Identification; 6: Protocol Compliance; 8: Continuing Review/Ongoing Benefit-Risk Assessment; 11: Records; 14: Quality Systems

12. Monitoring the trial

Sponsors generally perform site monitoring of a clinical trial to assure high quality trial conduct. The sponsor may perform such monitoring directly, or may utilize the services of an outside individual or organization (e.g., contract research organization [CRO]). The sponsor determines the appropriate extent and nature of monitoring based on the objective, purpose, design, complexity, size, blinding, and endpoints of the trial, and the risks posed by the investigational product.

The "on site" monitors review individual case histories in order to verify adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and verify adherence to GCP. In blinded studies, these monitors remain blinded to study arm assignment.

For an investigator-initiated study, the sponsor-investigator should consider the merits of arranging independent, external monitoring of the study, particularly when the study involves novel products or potential significant risks to subjects.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 8: Continuing Review; 11: Records; 14: Quality Systems.

13. Managing trial data

Within GCP, managing clinical trial data appropriately assures that the data are complete, reliable and processed correctly, and that data integrity is preserved. Data management includes all processes and procedures for collecting, handling, manipulating, analysing, and storing/archiving of data from study start to completion.

The sponsor bears primary responsibility for developing appropriate data management systems. The sponsor and the investigator share responsibility for implementing such systems to ensure that the integrity of trial data is preserved.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 11: Records; 14: Quality Systems.

See also Overview Processes 1: Protocol development; 2: Development of standard operating procedures; 3: Support systems and tools; 4: Trial information documents; 10: Trial data acquisition.

Data management systems should address (as applicable):

- data acquisition;
- confidentiality of data/data privacy;
- electronic data capture (if applicable);
- data management training for investigators and staff;
- completion of CRFs and other trial-related documents, and procedures for correcting errors in such documents;
- coding/terminology for adverse events, medication, medical histories;
- safety data management and reporting;
- data entry and data processing (including laboratory and external data);
- database closure;
- database validation;
- secure, efficient, and accessible data storage;
- data quality measurement (i.e., how reliable are the data) and quality assurance;
- management of vendors (e.g., CROs, pharmacies, laboratories, software suppliers, off-site storage) that participate directly or indirectly in managing trial data.

14. Quality assurance of the trial performance and data

Quality assurance (QA) verifies through systematic, independent audits that existing quality control systems (e.g., study monitoring: see GCP Process 12, *Monitoring the trial*; data management systems: see GCP Process 13, *Managing trial data*) are working and effective. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion.

Sponsors bear primary responsibility for establishing quality systems and conducting quality assurance audits.

See WHO GCP Principles 11: Records; 14: Quality Systems.

See also Overview Processes 2: Development of standard operating procedures; 10: Trial data acquisition: conducting the trial; 12; Monitoring the trial; and 13: Managing trial data.

15. Reporting the trial

The results of each controlled study involving an investigational product should be summarized and described in an integrated clinical study report containing clinical data and statistical descriptions, presentations, and analyses. The report should be complete, timely, well-organized, free from ambiguity, and easy to review.

The sponsor is responsible for preparing clinical study reports.

Such reports should generally include:

- a description of the ethical aspects of the study (e.g. confirmation that the study was conducted in accordance with basic ethical principles);
- a description of the administrative structure of the study (i.e. identification and qualifications of investigators/sites/other facilities);
- an introduction that explains the critical features and context of the study (e.g. rationale and aims, target population, treatment duration, primary endpoints);
- a summary of the study objectives;
- a description of the overall study design and plan;
- a description of any protocol amendments;
- an accounting of all subjects who participated in the study, including all important deviations from inclusion/exclusion criteria and a description of subjects who discontinued after enrollment;
- an accounting of protocol violations;
- a discussion of any interim analyses;

- an efficacy evaluation, including specific descriptions of subjects who were included in each efficacy analysis and listing of all subjects who were excluded from the efficacy analysis and the reasons for such exclusion;
- a safety evaluation, including extent of exposure, common adverse events and laboratory test changes, and serious or unanticipated or other significant adverse events including evaluation of subjects who left the study prematurely because of an adverse event or who died;
- a discussion and overall conclusions regarding the efficacy and safety results and the relationship of risks and benefits;
- tables, figures, and graphs that visually summarize the important results or to clarify results that are not easily understood;
- a reference list.

Where permitted, abbreviated or less detailed reports may be acceptable for uncontrolled or aborted studies.

See WHO GCP Principles 2: Protocol; 11: Records; see also ICH E3 (Structure and Content of Clinical Study Reports)

WHO Principles of GCP

Principle 1: Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles.

Principle 2: Research involving humans should be scientifically justified and described in a clear, detailed protocol.

Principle 3: Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.

Principle 4: Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the trial subjects.

Principle 5: Research involving humans should receive independent ethics committee/institutional review board (IEC/IRB) approval/favourable opinion prior to initiation.

Principle 6: Research involving humans should be conducted in compliance with the approved protocol

Principle 7: Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.

Principle 8: Research involving humans should be continued only if the benefit-risk profile remains favourable.

Principle 9: Qualified and duly licensed medical personnel (i.e., physician or, when appropriate, dentist) should be responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf.

Principle 10: Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

Principle 11: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Principle 12: The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Principle 13: Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing

Practice (GMP) and should be used in accordance with the approved protocol.

Principle 14: Systems with procedures that assure the quality of every aspect of the trial should be implemented.

WHO Principles of GCP

PRINCIPLE 1: ETHICAL CONDUCT

Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles enumerated below.

Ethical principles have been established by many national and international bodies, including:

1) The World Medical Association Declaration of Helsinki;

2) The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects;

and other guidelines (see References).

Application

Principle 1 is applied through

- design and approval of the protocol
- informed consent
- scientific and ethical review
- a favourable risk/benefit assessment
- fair and transparent procedures and outcomes in the selection of research subjects
- compliance with national and international laws, regulations, and standards.

Questions and Answers:

What is meant by "respect for persons" and how is it most directly implemented within GCP?

"Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection." (The Belmont Report; CIOMS, International Ethical Guidelines)

"Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied." (The Belmont Report)

In general, all individuals, including healthy volunteers, who participate as research subjects should be viewed as intrinsically vulnerable.

When some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons are likely to be more vulnerable to coercion or undue influence, additional safeguards should be included in the study to protect the rights and welfare of these subjects. These safeguards may include, but are not limited to: special justification to the ethical review committee that the research could not be carried out equally well with less vulnerable subjects; seeking permission of a legal guardian or other legally authorized representative when the prospective subject is otherwise substantially unable to give informed consent; including an impartial witness to attend the informed consent process if the subject or the subject's legally authorized representative cannot read; and/or additional monitoring of the conduct of the study.

Within GCP, the principle of "respect for persons" is most directly implemented through the process of informed consent. Included here is the provision that the subject (or subject's legally authorized representative) will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial. (See GCP Principle 7: *Informed Consent*)

What is meant by "beneficence" and how is it most directly implemented within GCP?

"**Beneficence** refers to the ethical obligation to maximize benefit and to minimize harm. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, **nonmaleficence** "do no harm". (CIOMS, International Ethical Guidelines)

The principle of "beneficence" bears a close relationship to the (GCP) "requirement that research be justified on the basis of a favourable risk/benefit assessment." (The Belmont Report)

"Risks and benefits of research may affect the individual subjects, … and society at large (or special groups of subjects in society)." "In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight." (The Belmont Report)

Within GCP, the principle of "beneficence" is most directly implemented through risk/benefit assessment during design and review (initial review as well as continuing review) of the study protocol. (See also WHO GCP Principles 3: Risk Identification; 4: *Benefit-Risk Assessment; 8: Continuing Review/Ongoing Benefit-Risk Assessment*)

What is meant by "justice" and how is it most directly implemented within GCP?

"… the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects." (The Belmont Report)

Justice in the selection of research subjects requires attention in two respects: the individual and the social.

"Individual justice in the selection of subjects requires that researchers exhibit fairness; thus, they should not offer potentially beneficial research to only some patients who are in favor or select only "undesirable" persons for risky research." (The Belmont Report)

Social justice relates to groups of subjects, including the involvement of vulnerable subjects or subject populations. "Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted" (The Belmont Report). "Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research, short-term or long-term… Subjects should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status, or gender unless there is a sound scientific reason to do otherwise." (CIOMS, International Ethical Guidelines, Commentary on Guideline 12)

Within GCP, the principle of "justice" is most directly implemented by considering procedures and outcomes for subject selection during the design and review of the study protocol as well as during recruitment and enrollment of study subjects. (See also WHO GCP Principles 2: *Protocol*, and 7: *Informed Consent*)

Implementation

The basic ethical principles of biomedical research are reflected in all GCP principles and processes, impacting on the role and responsibilities of each party within GCP. Each party participating in clinical research has responsibility for ensuring that research is ethically and scientifically conducted according to the highest standards. This includes the investigator(s) and site staff, the sponsor and sponsor's staff (including monitors and auditors), the ethics committee(s), the regulatory authority(-ies), and the individual research subjects.

For more information (including Roles and Responsibilities):

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000, Section 6.2)
- Follow-Up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000, Section 9)
- Ethical review of externally sponsored research, CIOMS, International Ethical Guidelines, Guideline 3)

For **clinical investigators**, refer to:

- Communications with the IRB/IEC (ICH E6, Section 4.4)
- Informed Consent of Trial Subjects (ICH E6, Section 4.8)
- Safety Reporting (ICH E6, Section 4.11)

For **sponsors**, refer to:

- Trial Design (ICH E6, Section 5.4)
- Notification/Submission to Regulatory Authority(ies) (ICH E6, Section 5.10)
- Safety Information (ICH E6, Section 5.16)

For **regulatory authorities**, refer to:

- WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP

- GCP Principle 2: Protocol
- GCP Principle 3: Risk Identification
- GCP Principle 4: Benefit-Risk Assessment
- GCP Principle 7: Informed Consent
- GCP Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment

Definitions for:

- Impartial Witness (ICH E6, 1.26)
- Informed Consent (ICH E6, 1.28)

Legally Acceptable Representative (ICH E6, 1.37)
Vulnerable Subjects (ICH E6, 1.61)
Well-being [of the Trial Subjects] (ICH E6, 1.62)

Clinical Trial Protocol and Protocol Amendment(s):
Selection and Withdrawal of Subjects (ICH E6, Section 6.5)
Ethics (ICH E6, Section 6.12)

PRINCIPLE 2: PROTOCOL

Research involving humans should be scientifically justified and described in a clear, detailed protocol.

"The experiment should be such as to yield fruitful results...unprocurable by other methods or means of study, and not random and unnecessary in nature." (The Nuremburg Code)

"The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol." (Declaration of Helsinki)

Application

Principle 2 is applied through development of a clear, detailed, scientifically justified and ethically sound protocol that (1) complies with requirements established by national and local laws and regulations, and (2) undergoes scientific and ethical review prior to implementation.

Questions and Answers

What is meant by "scientifically justified"?

The protocol must be carefully designed to generate statistically and scientifically sound answers to the questions that are being asked and meet the objective(s) of the study. The objective(s) should also justify the risk; that is, the potential benefits (if any) of participation in the study should outweigh the risks.

"A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results." (CIOMS, International Ethical Guidelines, Guideline 11)

What is a clear detailed protocol?

A protocol "describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could

be provided in other protocol referenced documents." (ICH E6, Section 1.44)

A protocol "provides the background, rationale, and objective(s) of a biomedical research project and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol." (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Glossary)

What information should be included in a study protocol?

The study protocol is the core document communicating trial requirements to all parties who have responsibility for approval, conduct, oversight, and analysis of the research.

GCP recognizes that certain essential elements should be included in the study protocol. These include but are not limited to:

- general information;
- background information;
- description of the trial objectives and purpose;
- description of the trial design;
- criteria for inclusion, exclusion, and withdrawal of study subjects;
- treatment information;
- methods and timing for assessing, recording and analysing data gathered on the investigational product;
- methods for obtaining safety information, including plans for safety monitoring;
- description of the statistical methods to be employed;
- description of ethical considerations relating to the trial;
- a statement related to permitting trial-related monitoring, audits, and inspection by the sponsor, IEC/IRB, and regulators, including direct access to source data/documents;

- means for obtaining informed consent and communication of information to prospective subjects.

What is a "protocol amendment"?

"A protocol amendment is a written description of a change(s) to or formal clarification of a protocol." (ICH E6, Section 1.45)

What types of changes may require formal amendment of the protocol?

Regional,[1] national, or local laws and regulations may require sponsors to prepare formal protocol amendments to describe any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Examples of changes that generally require formal amendment include, but are not limited to:

- changes in drug dosage or duration of exposure of individual subjects to an investigational product beyond that described in the current protocol;
- significant increase in the number of subjects under study or in the duration of the study;
- significant change in the study design, such as adding or dropping a control group; and
- addition of a new test or procedure that is intended to improve monitoring for or reduce the risk of a side effect or adverse event, or the dropping of a test intended to monitor safety.

[1] In this document, "regional" refers to supranational laws, regulations, or requirements, such as those adopted by the European Union.

What is the "investigator's brochure" and how does it relate to the protocol?

The investigator's brochure is a "compilation of the clinical and non-clinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects." (ICH E6, 1.36)

In general, the investigator's brochure provides more complete background information on the investigational product than is provided in the protocol. The investigator's brochure assists the investigator in interpreting and implementing the study protocol, and may be of particular importance in helping the investigator determine whether specific adverse events are unanticipated, and accordingly, when and how such events should be reported to the sponsor, IEC/IRB, and regulators.

What is meant by a well-controlled study?

A well-controlled study uses a design that permits a comparison of subjects treated with the investigational agent/intervention to a suitable control population, so that the effect of the investigational agent/intervention can be determined and distinguished from other influences, such as spontaneous change, "placebo" effects, concomitant therapy(ies)/intervention(s), or observer expectations.

What are some designs for controlled clinical studies?

Commonly used designs for controlled clinical studies include: placebo concurrent control; no-treatment concurrent control; dose-response concurrent control; active (positive) concurrent control; external control (including historical control); and combination (multiple control group) designs. (See ICH E10: Choice of Control Group and Related Issues in Clinical Trials)

"As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment"." (CIOMS, International Ethical Guidelines, Guideline 11)

What can be done to minimize bias in a clinical investigation?

Bias implies subjective or unfair distortion of judgment in favor of or against a person or thing. The purpose of conducting a clinical trial of an investigational product is to distinguish the effect of the investigational product from other factors, such as spontaneous changes in the course of the disease, placebo effects, or biased/subjective observation. Bias can be minimized in a clinical trial by designing well-controlled studies, by using blinding, and by using procedures to randomize subjects to the various study arms.

What is meant by "blinding" or "masking"?

Blinding or masking is "[a] procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s)." (ICH E6, 1.10)

When is unblinding of the trial by the investigator permissible? How should unblinding be accomplished (in those situations where it would be allowed)?

Unblinding may be necessary in the event of a medical emergency for a trial subject. Generally breaking the blind involves procedures specified in the study protocol that allow the investigator and/or sponsor to find out whether a particular subject received the investigational product, or received a comparator product or placebo, where applicable, while on the study.

"The investigator… should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s)." (ICH E6, Section 4.7)

What is meant by "randomization"?

Randomization is the "process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias." (ICH E6, 1.48)

"Randomization is the preferred method for assigning subjects to the various arms of the clinical trial unless another method, such as historical or literature controls, can be justified scientifically and ethically. Assignment to treatment arms by randomization, in addition to its usual scientific superiority, offers the advantage of tending to render equivalent to all subjects the foreseeable benefits and risks of participation in a trial." (CIOMS, International Ethical Guidelines, Guideline 11)

"The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol." (ICH E6, Section 4.7)

How should the protocol address reporting of adverse events?

The protocol should specify procedures for eliciting reports of, and for recording and reporting, adverse event and inter-current illnesses; the type and duration of the follow-up of subjects after adverse events, and the methods to be used in, and timing for, assessing, recording, and analysing safety parameters.

The protocol and investigator's brochure will assist the investigator and sponsor in determining whether an adverse event is "unexpected" and how it should be reported. Unexpected serious adverse drug reactions should be reported to the regulatory authority(ies) and to other investigators involved in the trial in accordance with applicable regulatory requirement(s).

Implementation

Sponsors are primarily responsible for (a) designing the clinical investigation, (b) developing the study protocol, investigator's brochure, and related materials to describe the procedures that will be followed, study endpoints, and data collection, and other study

requirements; and (c) ensuring that the protocol complies with applicable national and local laws and regulations.

Investigators may be consulted by the sponsor during protocol design or, in some cases, may personally contribute to the design of the protocol. Investigators are responsible for familiarizing themselves with the study protocol, investigator's brochure, and related materials to ensure that they are able to carry out the study in compliance with the specifications of the protocol.

IECs/IRBs are responsible for conducting ethical review of the study protocol. This also includes arranging for a scientific review or verifying that a competent body has determined that the research is scientifically sound. (See GCP Principle 5: *Review by IEC/IRB*)

Regulators bear responsibility for allowing a protocol to proceed in accordance with applicable laws and regulations. This may include prospective review of the protocol, the investigator's brochure and other relevant information. Where the protocol or investigator's brochure is inaccurate or materially incomplete, where the protocol does not adequately provide for the protection of subject rights and safety, or where the protocol is deficient in design to meet its stated objectives, the regulatory authority may require protocol modification or take action to disallow the protocol to proceed in accordance with applicable laws and regulations.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Clinical Trial Protocol and Protocol (sic) (ICH E6, Section 6)
- Investigator's Brochure (ICH E6, Section 7)
- Documentation (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 5.3)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)
- Adequate Resources (ICH E6, Section 4.2)
- Compliance with Protocol (ICH E6, Section 4.5)

Randomization Procedures and Unblinding (ICH E6, Section 4.7)
Safety Reporting (ICH E6, Section 4.11)
Clinical Trial Protocol and Protocol (*sic*) (ICH E6, Section 6)
Investigator's Brochure (ICH E6, Section 7)

For **sponsors**, refer to:

Trial Design (ICH E6, Section 5.4)
Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)
Notification/Submission to Regulatory Authorities (ICH E6, Section 5.10)
Clinical Trial Protocol and Protocol (*sic*) (ICH E6, Section 6)
Investigator's Brochure (ICH E6, Section 7)
Items to be Included in a Protocol (or Associated Documents) for Biomedical Research Involving Human Subjects (CIOMS, International Ethical Guidelines, Appendix 1)
WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995 (Section 2)

For **regulatory authorities**, refer to:

GCP Compliance Monitoring Programs by Regulatory Authorities (Good Clinical Practices: Document of the Americas, PAHO, Chapter 7)
WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP

GCP Principle 3: Risk Identification
GCP Principle 4: Benefit-Risk Assessment
GCP Principle 5: Review by IEC/IRB
GCP Principle 6: Protocol Compliance
GCP Principle 11: Records

Definitions for:

Investigator's Brochure (ICH E6, 1.36)
Protocol (ICH E6, 1.44)
Protocol Amendment (ICH E6, 1.45)

PRINCIPLE 3: RISK IDENTIFICATION

Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.

"The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment." (The Nuremberg Code)

"Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate animal experimentation." (Declaration of Helsinki)

"The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research... [T]he assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research." (The Belmont Report)

Application

Principle 3 is applied through:

- conducting a thorough search of available scientific information about the investigational product or procedure(s) (including findings from tests in laboratory animals and any previous human experience];
- developing the investigator's brochure, the study protocol, and the informed consent document to adequately, accurately, and objectively reflect the available scientific information on foreseeable risks and anticipated benefits.

Questions and Answers:

What is meant by "risk(s)" and "benefit(s)"?

"The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm. The term "benefit" is used in the research context to refer to something of positive value related to health or welfare." (The Belmont Report)

"Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked." (The Belmont Report)

"Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society)." "… In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight." (The Belmont Report) (See GCP Principle 1: *Ethical Conduct*)

How is identification of risks and benefits implemented within GCP and where may information about risks and benefits be obtained?

Within GCP, the identification of risks and benefits is undertaken as part of the scientific review that accompanies protocol development.

"… [M]edical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information and adequate laboratory and, where indicated, animal experimentation. Scientific review must consider, inter alia, the study design,

including the provisions for avoiding or minimizing risk and for monitoring safety." (CIOMS, International Ethical Guidelines, Commentary on Guideline 2)

Important to any scientific review is the critical selection and evaluation of that literature accessed from available scientific publications. However, it may also be important to review relevant unpublished data, particularly where such data raise concerns for subject safety.

What is non-clinical information?

Non-clinical information is information derived from non-clinical studies, defined as "Biomedical studies not performed on human subjects." (ICH, E6, 1.41)

The term includes in vivo (animal or plant studies) or in vitro (laboratory) experiments in which investigational products are studied in test systems under laboratory conditions to determine their safety. Regulators and others may require non-clinical studies to comply with standards for Good Laboratory Practice (GLP); such studies may be called or referred to as "GLP studies."

What is GLP (Good Laboratory Practice) and what is the relationship between GLP and GCP Principle 3?

The purpose of GLP is to assure the quality and integrity of non-clinical (notably animal) data submitted in support of research permits or marketing applications. In accordance with national/local laws and regulations, regulators may establish GLP standards for the conduct and reporting of non-clinical studies. GLP standards include requirements for: organization and management of the testing facility, qualifications of personnel and the study director, quality assurance units, characteristics of animal care facilities, laboratory operation areas, and specimen and data storage facilities, equipment maintenance, standard operating procedures, characterization of test and control articles, protocols, study conduct, reports, and record keeping.

In accordance with national/local laws and regulations, compliance with GLP may be a requirement for the acceptance of animal toxicology studies in support of human testing. Where not required by national/local laws and regulations, GLP standards provide important guidance to the conduct of quality animal toxicology studies.

What does the term "clinical information" include?

Clinical information here refers to information derived from prior clinical study or experience. A clinical study is defined as "[a]ny investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous." (ICH E6, 1.12)

What is meant by "foreseeable" and "anticipated"?

The terms "foreseeable" and "anticipated" connote knowledge that is available or predictable at the time of protocol review. Implicit in these terms is the obligation to conduct a thorough search of scientific literature contemporaneous to the time of initial protocol review and the obligation to keep apprised of significant new findings on risks and/or benefits that become available as the protocol proceeds.

Implementation

The responsibility for implementing this principle is shared by sponsors, investigators, IECs/IRBs, and regulators:

The **sponsor** generally conducts the literature review to ensure that there is sufficient information available to support the proposed clinical trial in the population to be studied and that there is sufficient safety and efficacy data to support human exposure to the product. The sponsor may need to conduct pre-clinical studies to ensure

there is sufficient safety and efficacy data to support human exposure. The sponsor should summarize available information about the procedure/product in the investigator's brochure, and accordingly set forth the design of the study in the protocol. In general, it is important that the sponsor develop a comprehensive, accurate and complete investigator's brochure, as this is a principal means of communicating vital safety and scientific information to the investigator and, in turn, to the IEC/IRB.

Review of the protocol, investigator's brochure, and other relevant information enables the **IECs/IRBs** to (1) determine whether the benefits outweigh the risks, (2) understand the study procedures or other steps that will be taken to minimize risks, and (3) ensure that the informed consent document accurately states the potential risks and benefits in a way that will facilitate comprehension by all study subjects, with particular attention to vulnerable groups.

Investigators must be knowledgeable of the protocol, investigator's brochure and other relevant information regarding potential risks and benefits, and must be able to adequately, accurately and objectively identify the potential risks and benefits to subjects. Investigators may need to do some additional literature search beyond that provided by the sponsor. Investigators should also be thoroughly familiar with the appropriate use of the trial product(s)/procedures and should take the necessary steps to remain aware of all relevant new data on the investigational product, procedure, or method that becomes available during the course of the clinical trial.

Regulators bear responsibility for allowing a protocol to proceed in accordance with existing national laws/regulations or internationally accepted standards. This may include prospective review of the protocol, the investigator's brochure and other relevant information to ensure that risk(s) and benefit(s) are accurately identified and justify allowing the protocol to proceed. As appropriate, adopted national standards should address additional national or regional racial, cultural, or religious standards/issues not otherwise covered by the international standards. In accordance with national/local laws and regulations, regulators may establish standards for the conduct of

non-clinical studies, review non-clinical and clinical data submitted in support of research permits or marketing applications, and/or inspect facilities that conduct non-clinical and clinical studies.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Procedures (ICH E6, Section 3.3)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)
- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)

For **clinical investigators**, refer to:

- Investigator's Brochure (ICH E6, Section 7)
- Clinical Trial Protocol, General Information (ICH E6, Section 6)

For **sponsors**, refer to:

- Investigator's Brochure (ICH E6, Section 7)
- Clinical Trial Protocol (ICH E6, Section 6)
- UNDP/World Bank WHO Special Programme for Research and Training in Tropical Diseases (TDR) "Handbook on Good Laboratory Practice (GLP): Quality Practices for Regulated Non-Clinical Research and Development" (September 2000)
- Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3)
- Preclinical Testing of Biotechnology-Derived Pharmaceuticals (ICH S6)
- Literature review ("Clinical Investigation of medical devices for human subjects," ISO 14155-1, Part 1, Annex A)

For **regulatory authorities**, refer to:

- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995
- UNDP/World Bank WHO Special Programme for Research and Training in Tropical Diseases (TDR) "Handbook on Good Labora-

tory Practice (GLP): Quality Practices for Regulated Non-Clinical Research and Development" (September 2000)

Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3)

Preclinical Testing of Biotechnology-Derived Pharmaceuticals (ICH S6)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 1: Ethical Conduct

GCP Principle 2: Protocol

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 7: Informed Consent

Definitions for:

Investigator's Brochure (ICH E6, 1.36)

Nonclinical Study (ICH E6, 1.41)

Protocol (ICH E6, 1.44)

Protocol Amendment (ICH E6, 1.45)

PRINCIPLE 4: BENEFIT-RISK ASSESSMENT

Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well being of the research subjects.

"The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment." (The Nuremberg Code)

"Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research." (Declaration of Helsinki)

"For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized." (CIOMS, International Ethical Guidelines, Guideline 8)

"It is commonly said that benefits and risks must be 'balanced' and shown to be 'in a favourable ratio.'… Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit... It should also be determined whether … estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies." (The Belmont Report)

"… Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures… .When research involves significant risk of serious impairment, review committees should be extraordinarily

insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or in some rare cases, to the manifest voluntariness of the participation)… " (The Belmont Report)

"… Scientific review must consider inter alia, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety." (CIOMS, International Ethical Guidelines, Commentary on Guideline 2)

"Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society)." "… In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight." (The Belmont Report)

"In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society." (Declaration of Helsinki)

Application

Principle 4 is applied through appropriate study design and through ethical, scientific, and, where applicable, regulatory review of the study protocol prior to its initiation.

Questions and Answers

Who is responsible for determining that the risk/benefit profile of a study is acceptable or unacceptable?

Within GCP, the sponsor of the study, the investigator(s), IECs/IRBs, and the regulatory authority(-ies) each have responsibilities for evaluating the risk/benefit profile of a study (see Implementation, below). In accordance with applicable laws and regulations, the regulatory authority may stop a study from proceeding or require modifications to the protocol based on an unacceptable risk/benefit profile. The IEC/IRB has authority to issue an approval/favourable opinion; require modifications prior to approval/favourable opinion; issue a disapproval/negative opinion; or terminate/suspend a prior approval/favourable

opinion. An investigator may decide either to participate or not participate in a study based on his/her assessment of the risk/benefit profile. The sponsor may decide either not to initiate or to terminate/suspend a trial where the risk/benefit profile is unacceptable.

When should a risk/benefit determination be performed?

A risk/benefit determination should be performed prior to study initiation as well as periodically during the study (see also GCP Principle 8: *Continuing Review/Ongoing Benefit-Risk Assessment*).

What if the risk-benefit profile of a study appears favourable from a national, societal, institutional, or scientific standpoint but unfavourable to the participating research subjects?

The most important considerations in a study are those related to the rights, safety, and well-being of the trial subjects. "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society." (Declaration of Helsinki)

What about financial reimbursements to research subjects?

Financial reimbursements to subjects are distinct from any benefits contributing to the risk-benefit analysis.

Where applicable laws and regulations allow, financial reimbursements may be provided to subjects for participation in a study. Where no requirements exist, fair compensation should be provided in an appropriate manner after consultation with the relevant institutions/organizations. Such reimbursements are generally viewed as part of the recruitment process rather than as benefits of the study. However, at the time of initial review, the IEC(s)/IRB(s) should review both the amount of the financial reimbursement(s) and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. The reimbursements provided should not be so large as to unduly induce subjects to enroll in the

study or to stay in the study when they would otherwise withdraw. Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. The reimbursements should not replace adequate insurance to be provided by the sponsor against claims for any trial-related injuries.

Implementation

The responsibility for implementing this principle is shared by sponsors, investigators, IECs/IRBs, and regulators.

The **sponsor** should design research studies to ensure that risks to subjects are minimized.

The **investigator(s)** should review the investigator's brochure and other relevant risk and benefit information in making a decision to conduct the study. The investigator is also responsible for providing adequate, accurate, and objective information on risks and benefits during informed consent of study subjects.

Prior to study initiation, the IEC(s)/IRB(s) should review the protocol, investigator's brochure, and other relevant information to (1) understand the study procedures or other steps that will be taken to minimize risks, (2) understand the potential benefits (if any) and determine whether those benefits outweigh the anticipated risks, and (3) ensure that the informed consent document accurately states the potential risks and benefits in a way that will allow study subjects to understand what they are undertaking.

Regulators bear responsibility for allowing a protocol to proceed in accordance with applicable laws and regulations. This may include prospective review of the protocol, the investigator's brochure, and other relevant information to ensure that risk(s) and benefit(s) are accurately identified and justify allowing the protocol to proceed. The regulatory authority may require modification to a protocol as a condition to its proceeding and/or may suspend or terminate a protocol based on an unacceptable risk/benefit profile in accordance with applicable laws and regulations.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Procedures (ICH E6, Section 3.3)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)
- Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)
- Inducement to participate in research (CIOMS International Ethical Guidelines, 2002, Guideline 7)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)
- Clinical Trial Protocol, General Information (ICH E6, Section 6)
- Investigator's Brochure (ICH E6, Section 7)
- Inducement to participate in research (CIOMS International Ethical Guidelines, 2002, Guideline 7)

For **sponsors**, refer to:

- Notification/Submission to Regulatory Authority(ies) (ICH E6, Section 5.10)
- Clinical Trial Protocol, General Information (ICH E6, Section 6)
- Investigator's Brochure (ICH E6, Section 7)

For **regulatory authorities**, refer to:

- WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP

- GCP Principle 2: Protocol
- GCP Principle 3: Risk Identification
- GCP Principle 7: Informed Consent
- GCP Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment

Definitions for:

Applicable Regulatory Requirement(s) (ICH E6, 1.4)

Approval (in relation to institutional review boards [IRBs]) (ICH E6, 1.5)

Informed Consent (ICH E6, 1.28)

Investigator's Brochure (ICH E6, 1.36)

PRINCIPLE 5: REVIEW BY IEC/IRB

Research involving humans should receive independent ethics committee/institutional review board (IEC/IRB) approval/ favourable opinion prior to initiation.

The "… protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed… " (Declaration of Helsinki)

"Failure to submit a protocol to the committee should be considered a clear and serious violation of ethical standards." (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

Application

Principle 5 is applied through protocol review by an IEC/IRB that is constituted and operating in accordance with GCP and applicable national/local laws and regulations.

Questions and Answers

What is the objective of obtaining IEC/IRB review of the protocol?

It is the IEC/IRB "… whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the trial protocol… " (ICH E6, 1.27)

The principal focus of the IEC/IRB is ethical review of the protocol. However, "… [s]cientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is ipso facto unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of

subjects' and researchers' time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out or arrange for a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound… " (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

Review by the IEC/IRB also helps ensure that the research is evaluated by a party that is independent of the trial. "The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review." (CIOMS, International Ethical Guidelines, Guideline 2)

How does the composition and operation of the IEC/IRB within GCP promote its independence?

Within GCP, "the IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include: (a) [a]t least five members, (b) [a]t least one member whose primary area of interest is in a nonscientific area, (c) [a]t least one member who is independent of the institution/trial site." (ICH E6, Section 3.2)

In its operations, "[o]nly those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter." (ICH E6, Section 3.2).

"To maintain the review committee's independence from the investigators and sponsors and to avoid conflict of interest, any member with a special or particular, direct or indirect, interest in a proposal should not take part in its assessment if that interest could subvert the member's objective judgment. Members of ethical review committees should be held to the same standard of disclosure as scientific and medical research staff with regard to financial or other interests that could be construed as conflicts of interest. A practical

way of avoiding such conflict of interest is for the committee to insist on a declaration of possible conflict of interest by any of its members. A member who makes such a declaration should then withdraw, if to do so is clearly the appropriate action to take, either at the member's own discretion or at the request of the other members. Before withdrawing, the member should be permitted to offer comments on the protocol or to respond to questions of other members." (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

"The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC." (ICH E6, Section 3.2)

"[T]here should be a predefined method for arriving at a decision (e.g., by consensus, by vote); it is recommended that decisions be arrived at through consensus, where possible; when a consensus appears unlikely, it is recommended that the EC vote." (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 7, *Decision Making*)

Within GCP, what is meant by "prior" opinion by the IEC/IRB?

GCP requires that "[b]efore initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects." (ICH E6, Section 4.4)

"The IRB/IEC should establish, document in writing, and follow its procedures, which should include: … [s]pecifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial." (ICH E6, Section 3.3)

What is the authority of the IEC/IRB with respect to rendering a decision/opinion on the protocol?

The IEC/IRB may render a decision/opinion that can be positive, conditional, or negative. Regardless of the nature of the decision/opinion, it should be documented and communicated in writing to the applicant.

Approval/favourable opinion. This positive decision/opinion is required prior to initiating a new protocol and prior to making changes in a protocol that has previously received an approval/favourable opinion. In communicating this decision/opinion to the applicant, the IEC/IRB should include a statement of the responsibilities of the applicant.

Modifications required prior to its approval/favourable opinion. This is a conditional decision/opinion that requires response from the applicant and consideration of the applicant's response by the IEC/IRB. Implementation of the protocol/protocol change(s) may not occur until required modifications are made and the IEC/IRB has rendered an approval/favourable opinion based on these modifications. In the case of a conditional decision/opinion, any requirements of the IEC/IRB, including clear suggestions for revision and the procedure for having the application re-reviewed should be specified in written communication to the applicant. The written communication should emphasize that no study activities requiring IEC/IRB approval/favourable opinion may take place under a conditional decision.

Disapproval/negative opinion. This negative decision/opinion can apply to the disapproval/negative opinion of a new protocol or the disapproval/negative opinion of changes to an ongoing protocol. Communication of a disapproval/negative opinion should include clearly stated reason(s) for the negative decision/opinion.

Termination/suspension of any prior approval/favourable opinion. This negative decision/opinion constitutes an action by the IEC/IRB to terminate or suspend its prior approval/favourable opinion. Written communication by the IEC/IRB should include clearly stated reason(s) for this decision/opinion.

Implementation

The responsibility for implementing this principle is shared by IEC(s)/IRB(s), investigators, sponsors, and regulators.

A properly constituted and operational **IEC/IRB** reviews the protocol (and/or any proposed changes to the protocol) and provides the investigator with a written decision/opinion. IEC/IRB written procedures should ensure that no subject be admitted to a trial and no deviations from, or changes to, the protocol be initiated before the IEC/IRB issues its approval/favourable opinion.

Investigators submit the study protocol to their IEC(s)/IRB(s) and are responsible for securing an approval/favourable opinion prior to admitting any subjects to the trial. Investigators should not implement any deviation from, or changes to, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IEC(s)/IRB(s) of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects. (See GCP Principle 6, *Protocol Compliance*)

The **sponsor** develops the protocol, selects qualified investigators/institutions, and confirms that each investigator has had the study protocol reviewed by an IEC/IRB and received IEC/IRB approval/favourable opinion.

In accordance with applicable laws/regulations, **regulators** may inspect the investigator(s), sponsor(s), and/or IEC(s)/IRB(s) to ensure compliance with IEC/IRB review requirements. Regulators should also encourage IECs/IRBs to communicate with them directly on issues or concerns they may encounter in their review of human trials.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)
Composition, Functions, and Operations (ICH E6, Section 3.2)
Procedures (ICH E6, Section 3.3)
Records (ICH E6, Section 3.4)

Constituting an EC (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 4)

Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6)

Decision-Making (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 7)

Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)

Follow-Up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)

Documentation and Archiving (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 10)

Ethical review committees (Guideline 2) and Ethical review of externally sponsored research (Guideline 3), (CIOMS International Ethical Guidelines, 2002)

For **clinical investigators**, refer to:

Communication with IRB/IEC (ICH E6, Section 4.4)

For **sponsors**, refer to:

Confirmation of Review by IRB/IEC (ICH E6, Section 5.11)

For **regulatory authorities**, refer to:

Surveying and Evaluating Ethical Review Practices (a complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research), WHO, 2002

See also:

Discussion of the WHO Principles of GCP:

GCP Principle 2: Protocol

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 6: Protocol Compliance

GCP Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment

Definitions for:

Approval (in relation to institutional review boards (IRBs)) (ICH E6, 1.5)

Independent Ethics Committee (IEC) (ICH E6, 1.27)

Institutional Review Board (IRB) (ICH E6, 1.31)

Opinion (in relation to Independent Ethics Committee) (ICH E6, 1.42)

PRINCIPLE 6: PROTOCOL COMPLIANCE

Research in humans should be conducted in compliance with the approved protocol.

Once the IEC/IRB gives its approval/favourable decision on the protocol, it is essential that the trial be conducted in compliance with that protocol so that the decision on the ethical acceptability of the trial remains valid.

"The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s))." (ICH E6, Section 4.5)

Application

Principle 6 is applied through: 1) verifiable investigator adherence to the protocol requirements; 2) submission of any protocol changes to the sponsor and to the IEC/IRB (with approval/favourable opinion) prior to their implementation; and 3) effective monitoring of the study by the sponsor.

Questions and Answers

What does conducting the trial in compliance with the protocol mean?

Compliance with the protocol means performing all of the study activities covered by the protocol (i.e. identifying, informing, selecting, treating, observing, recording, withdrawing, terminating, reporting, analysing) in the precise manner specified in the approved protocol.

It is especially important that those study activities most critical to ensuring the rights and well being of subjects and the quality and integrity of safety and efficacy data are carried out strictly according to the approved protocol, including but not limited to:

- informing subjects fully and obtaining their agreement and documented consent before enrolling them in the study;
- selecting subjects in accordance with the inclusion and exclusion criteria;
- treating subjects with the investigational product as specified in the protocol;
- observing and accurately recording key safety and efficacy endpoint data;
- reporting all serious adverse events (SAEs) to the sponsor immediately except for those SAEs that the protocol or other document (e.g. investigator's brochure) identifies as not needing immediate reporting.

How is compliance with the protocol ensured and documented within GCP?

The first step in promoting protocol compliance is the development of a well-designed, clearly written protocol. (See GCP Principle 2: *Protocol*)

To ensure and document understanding of the protocol "[t]he sponsor should obtain the investigator's/institution's agreement: (a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC..." (ICH E6, Section 5.6)

"... The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement" to conduct the study in compliance with the protocol. (ICH E6, Section 4.5; see also Section 5.6)

Once the study is underway, compliance with the protocol is principally ensured through the investigator's supervision and through the sponsor's monitoring of the study. Within GCP, the purposes of trial monitoring explicitly include verifying that "... [t]he conduct of the trial is in compliance with the currently approved protocol/amendment(s),

with GCP, and with applicable regulatory requirement(s)." (ICH E6, Section 5.18)

"The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication." (ICH E6, Section 5.18)

"Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance." (ICH E6, Section 5.20)

"… If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial… " (ICH E6, Section 5.20)

The IEC/IRB may also terminate or suspend any prior approval/favourable opinion. Within GCP, this would include the authority to terminate or suspend an approval/favourable opinion when information is received that the study is not being conducted in compliance with the protocol or other requirements of the IEC/IRB.

Who is responsible for compliance with the protocol?

The investigator has direct contact with study subjects and bears primary responsibility for complying with the provisions of the protocol. The investigator also bears responsibility to personally supervise all study staff and ensure their compliance with the protocol.

The sponsor has responsibility to monitor the study and ensure the investigator and site staff comply with the protocol.

Implementation

The responsibility for implementing this principle is shared by IEC(s)/IRB(s), investigators, sponsors, and regulators.

IEC/IRB written procedures should ensure that no subject be admitted to a trial and no deviations from, or changes of, the protocol be initiated before the IEC/IRB issues its approval/favourable opinion.

Investigators should be thoroughly familiar with the protocol and are responsible for conducting the trial in compliance with the protocol. Investigators should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB(s)/IEC(s) of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects.

The **sponsor** monitors the study to ensure investigator compliance with the protocol and takes action to secure compliance or terminate the trial in the case of noncompliance. If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. All parties, including the IEC/IRB, should be notified in such cases.

In accordance with applicable laws/regulations, **regulators** may inspect the investigator(s) or sponsor to ensure compliance with protocol adherence requirements. Regulators should be promptly notified when a sponsor identifies serious and/or persistent noncompliance on the part of an investigator/institution leading to termination of the investigator's/institution's participation in a study.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)
Procedures (ICH E6, Section 3.3)

For **clinical investigators**, refer to:

Compliance with Protocol (ICH E6, Section 4.5)

For **sponsors**, refer to:

Record Access (ICH E6, Section 5.15)
Monitoring (ICH E6, Section 5.18)
Noncompliance (ICH E6, Section 5.20)

For **regulatory authorities**, refer to:

WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP:

GCP Principle 2: Protocol

Definitions for:

Compliance (in relation to trials) (ICH E6, 1.15)

Monitoring (ICH E6, 1.38)

PRINCIPLE 7: INFORMED CONSENT

Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.

"In particular, no one shall be subjected without his free consent to medical or scientific experimentation." (United Nations International Covenant on Civil and Political Rights)

"The subjects must be volunteers and informed participants in the research project." (Declaration of Helsinki)

"...[T]here is widespread agreement that the consent process can be analysed as containing three elements: information, comprehension, and voluntariness." (The Belmont Report)

"For all biomedical research involving humans, the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee." (CIOMS, International Ethical Guidelines, Guideline 4)

"Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

Application

Principle 7 is applied through a process of informing and ensuring comprehension by study subjects (and/or their legally authorized representatives) about the research and obtaining their consent, including appropriate written informed consent.

Questions and Answers

What is meant by "freely given" consent or "voluntary" participation in an investigation? How is this implemented within GCP?

"Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

"An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence." (The Belmont Report)

"Unjustifiable pressures usually occur when persons in positions of authority or commanding influence – especially where possible sanctions are involved – urge a course of action for a subject." "… [U]ndue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled." (The Belmont Report)

"The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree or by fear of disapproval or retaliation if they refuse." (CIOMS, International Ethical Guidelines, Commentary on Guideline 13)

"… The researcher should give no unjustifiable assurances about the benefits, risks or inconveniences of the research, for example, or induce a close relative or a community leader to influence a prospective subject's decision." (CIOMS, International Ethical Guidelines, Commentary on Guideline 6)

What is meant by "in accordance with national culture(s) and requirements"?

"In some cultures, an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

What is meant by "informed" consent?

"Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

Who may administer informed consent?

The person who conducts the consent interview should be knowledgeable about the study and able to answer questions. Some sponsors and some IECs/IRBs require the clinical investigator to personally conduct the consent interview. If someone other than the clinical investigator conducts the interview and obtains consent, the clinical investigator should ensure that this responsibility is formally delegat-

ed to that individual, and that the person so delegated is qualified and receives appropriate training to perform this activity.

What "information" should be given to study subjects in accordance with GCP?

GCP recognizes that certain essential elements of informed consent should be included in the informed consent discussion, the written informed consent form, and any other information to be provided to subjects who participate in the study. All information must be communicated in a comprehensive and understandable manner to the trial subject. This includes, but is not limited to:

- title of the protocol;
- identity of the sponsor;
- identiy of the clinical investigator and institutional affiliation of the investigator;
- source of research funding (e.g., public, private, or both);
- that the trial involves research;
- that the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled;
- the purpose of the trial;
- the trial treatment(s) and the probability for random assignment to each treatment;
- the trial procedures to be followed, including all invasive procedures;
- the subject's responsibilities;
- those aspects of the trial that are experimental;
- the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus or nursing infant;

- the reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this;
- the alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks;
- the compensation and/or treatment available to the subject in the event of trial-related injury;
- the anticipated prorated money or other forms of payment (e.g., material goods), if any, to the subject for participating in the trial;
- the anticipated expenses, if any, to the subject for participating in the trial. This may include expenses to the subject for routine medical care for conditions that are not within the scope of the research;
- that the monitor(s), the auditor(s), the IEC/IRB, and the regulatory authority(-ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally authorized representative is authorizing such access;
- that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential;
- the potential risks should confidentiality measures be compromised (e.g., stigma, loss of reputation; potential loss of insurability);
- that the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial;

- the person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury;
- the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated;
- the expected duration of the subject's participation in the trial;
- the approximate number of subjects involved in the trial.

"… Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator." (The Belmont Report)

Due consideration should be given to obtaining consent for the collection and/or use of biological specimens, including future purposes. Guidance is developing in this area (see CIOMS International Ethical Guidelines; CIOMS Report on Pharmacogenetics – Towards improving treatment with medicines, 2005; Council of Europe [CDBI] Additional Protocols to Oviedo Convention, 2005).

What is meant by "comprehension"? That is, how do investigators ensure that subjects understand information about the study, and how is this implemented in accordance with GCP?

"The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice." (The Belmont Report)

"Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information, whether orally or in writing, in language that

suits the individual's level of understanding. The investigator must bear in mind that the prospective subject's ability to understand the information necessary to give informed consent depends on that individual's maturity, intelligence, education and belief system… … The investigator must then ensure that the prospective subject has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

What is meant by "vulnerable persons"?

In general, all individuals, including healthy volunteers, who participate as research subjects should be viewed as intrinsically vulnerable because:

1) during the course of the study they are (or may be) exposed to an investigational product about which the safety and efficacy is unknown or incompletely understood; and
2) there may be other factors – social, cultural, economic, psychological, medical – that may adversely affect the subjects' ability to make rational, objective choices that protect their own interests, but which may not be readily apparent to the researcher.

Some vulnerabilities may be readily identified because they are obvious (e.g., institutionalized subjects, individuals with diminished mental capacities) or relevant to the research (e.g., children participating in a paediatric vaccine trial). Other vulnerabilities of subjects may not be so readily identified (e.g. subjects who are homeless or economically disadvantaged). Subjects may also become more or less vulnerable throughout a study as circumstances about their health status and lives change.

"Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength,

or other needed attributes to protect their own interests." (CIOMS, International Ethical Guidelines, Commentary on Guideline 13)

Examples of vulnerable persons include, but are not limited to: children, individuals with diminished mental capacity, prisoners, institutionalized persons (including orphans), patients in emergency situations, the economically disadvantaged, individuals who cannot give consent.

"One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition." (The Belmont Report)

What special protections are required to enable vulnerable populations to participate in research?

"For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons." (Declaration of Helsinki)

"Special provision may need to be made when comprehension is severely limited … .. for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g. infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving

them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm." (The Belmont Report)

"The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest." (The Belmont Report)

How is informed consent documented? Is getting the subject (or the subject's representative) to sign a consent document all that is necessary? How should the process be documented throughout the study?

"Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject, and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

"Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent

form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so. … .When consent has been obtained orally, investigators are responsible for providing documentation or proof of consent." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

When material changes occur in the conditions or the procedures of a study, and also periodically in long-term studies, the investigator should once again seek informed consent from the subjects… " (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

Is it ethical to include subjects who are unable to consent?

"Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee… " (Declaration of Helsinki)

"When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them." (CIOMS, International Ethical Guidelines, Guideline 9)

When should informed consent be obtained? What is meant by "prior to trial participation"?

Informed consent should be obtained from each subject or the subject's legally authorized representative prior to involving the subject

in any study-specific activities. This includes diagnostic or other tests that are administered solely for determining the subject's eligibility to participate in the research.

Implementation

The responsibility for implementing and overseeing the informed consent process is shared by sponsors, clinical investigators, IECs/IRBs, and regulatory authorities.

IECs/IRBs are responsible for:

- reviewing the informed consent document to ensure that it is accurate, complete, and written in language that will be understood by the potential study subjects and translated into other languages, as appropriate;
- requesting modifications to the informed consent document, as appropriate; and
- at their discretion, observing the consent process and the research.

Investigators are responsible for ensuring that:

- staff responsible for obtaining informed consent receive appropriate training, both in research ethics and in the requirements of the specific study protocol;
- the IEC/IRB reviews and approves the informed consent form and other written information to be used in the study prior to its use; and
- informed consent is obtained from each subject or the subject's representative prior to involving the subject in any study related activities, including diagnostic or other tests that are administered solely for determining the subject's eligibility to participate in the research.

Sponsors are responsible for monitoring the research at study sites to ensure that sites are obtaining informed consent from all study subjects prior to subjects' inclusion in the research study.

In accordance with national and local laws and regulations, **regulators** may inspect the various parties who conduct or oversee research to ensure that they are complying with applicable laws and regulations and enforcing non-compliance. For example, regulators may inspect IECs/IRBs to ensure that informed consent documents and procedures are appropriately reviewed; they may inspect clinical investigators to determine whether informed consent was obtained prior to subjects' inclusion in the study; they may inspect sponsors to ascertain whether studies are being appropriately monitored.

For more information (including Roles and Responsibilities)

For **all parties**:

- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guidelines 4, 5, 6, 13, 14, 15, and 16;
- Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Documentation (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 5.3)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)
- Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
- Surveying and Evaluating Ethical Review Practices (a complementary guideline to the Operational Guidelines for Ethics Committees That Review Biomedical Research), WHO, 2002

For **clinical investigators**, refer to:

- Communication with IRB/IEC (ICH E6, Section 4.4)
- Informed Consent of Trial Subjects (ICH E6, Section 4.8)

For **sponsors**, refer to:

- Confirmation of Review by IRB/IEC (ICH E6, Section 5.11)
- Monitoring (ICH E6, Section 5.18)

For **regulatory authorities**, refer to

- Surveying and Evaluating Ethical Review Practices (a complementary guideline to the Operational Guidelines for Ethics Committees That Review Biomedical Research), WHO, 2002
- A Guide to Clinical Investigator Inspections (Good Clinical Practices: Document of the Americas, PAHO, Annex 4)

See also:

Discussion of the WHO Principles of GCP

- GCP Principle 1: Ethical Conduct
- GCP Principle 4: Benefit-Risk Assessment

Definitions for:

- Informed Consent (ICH E6, 1.28)
- Legally Acceptable Representative (ICH E6, 1.37)
- Vulnerable Subjects (ICH E6, 1.61)
- Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 8: CONTINUING REVIEW/ ONGOING BENEFIT-RISK ASSESSMENT

Research involving humans should be continued only if the benefit-risk profile remains favourable.

"During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experimental subject." (The Nuremburg Code)

"… The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of its progress." (CIOMS, International Ethical Guidelines, Guideline 2)

"… The committee has the right to monitor ongoing trials… " (Declaration of Helsinki)

"… Clinical trial sponsors should develop a process to assess, evaluate and act on safety information during drug development on a continuous basis in order to ensure the earliest possible identification of safety concerns and to take appropriate risk minimization steps. Such steps can include modification of study protocols, to incorporate strategies to ensure that clinical trial participants are not exposed to undue risk." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. *Identification and Evaluation of Risk from Clinical Trial Data*)

Application

Principle 8 is applied through development and implementation of processes for evaluating risks and benefits of the research as additional information becomes available during the course of the study. Principle 8 encompasses (1) safety monitoring of the study by investigator(s) and sponsor (including use of a data and safety monitoring board [DSMB], where appropriate); (2) reporting serious unexpected adverse events or other unanticipated risks to the sponsor, IEC/IRB, and regulators; (3) review by the IEC/IRB of any unan-

ticipated risks as they occur, or at scheduled intervals appropriate to the degree of risk; (4) revising the protocol, investigator's brochure, and/or informed consent document as needed, and suspending or terminating studies if necessary to protect the rights and welfare of study subjects.

Questions and Answers:

How are unanticipated risks identified during the course of a study?

Investigators and site staff are often the first to discover or observe unanticipated risks to subjects (e.g., serious unexpected adverse events; significant breaches of confidentiality) during the course of a study. Sponsors may also identify unanticipated risks to subjects in the course of study monitoring or from planned interim data analyses.

"The frequent review of serious and special interest adverse events, as well as overall assessment of all AEs, regardless of seriousness, causality, or expectedness, should be performed periodically: (1) *ad hoc*, for serious and special interest AEs, (2) routine, periodic general review of all data, whose frequency will vary from trial to trial and from development program to development program and depend on many factors, and (3) reviews triggered by specific milestones established for a trial or a program (e.g., numbers of completed patients, end-of-trial, end-of program, preparation of integrated summary of safety, and a marketing application." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. *Frequency of Review of Safety Information*)

How should serious unexpected adverse events (SAEs) be reported and to whom?

"All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. investigator's brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly

by detailed written reports." "… The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC." (ICH E6, Section 4.11)

"In addition to the usual criteria for an expedited report, adverse events that are not deemed to be drug-related but are considered to be protocol related should also be reported in an expedited fashion if they are serious." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. *Regulatory Reporting and other Communication of Safety Information from Clinical rials*)

Who is responsible for reviewing the benefit-risk profile of the investigational product(s) while the study is proceeding?

Within GCP, the sponsor has primary responsibility for the ongoing safety evaluation of the investigational product(s) and should promptly notify all concerned investigator(s), institution(s), and the regulatory authority(ies) of information that could adversely affect the safety of subjects, the conduct of the trial, or alter the IEC/IRB approval/favourable opinion to continue the trial. Such reviews may be performed by the sponsor's staff (e.g., physicians, statisticians) or by an independent data and safety monitoring board (DSMB), if one is established (see below).

The IEC/IRB is also responsible for "… following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research." (See "Follow-up", Section 9, *WHO Operational Guidelines for Ethics Committees that Review Biomedical Research*)

How are follow-up reviews carried out?

Sponsors generally monitor trials to ensure that (1) the study is being conducted according to the approved protocol, GCP, and applicable regulatory requirements, and (2) all data, including adverse event reports are accurately and completely recorded and reported. The sponsor also employs qualified individuals (e.g., physicians, statisti-

cians) as appropriate, throughout all stages of the trial process, to analyse data and prepare interim reports about the progress of the trial and the benefits and risks of the investigational product. The sponsor may also establish an independent data and safety monitoring board (DSMB, see below) to review the accumulating data. The sponsor should ensure that significant new information that arises about a clinical trial is promptly shared with all investigators, regulatory authorities and IECs/IRBs.

The IEC/IRB generally establishes procedures for (1) ensuring that new information that may adversely affect the safety of subjects or the conduct of the trial (e.g. serious/unexpected adverse events; unanticipated risks) are communicated to the IEC/IRB; (2) conducting the follow-up review; and (3) communicating decisions/opinions to the investigator.

When or how often should a benefit-risk determination be performed?

An evaluation should be carried out promptly following receipt of significant new information that may adversely affect the safety of subjects or the conduct of the trial. Generally, such new information is supplied by the clinical investigator(s), but it may also come from a DSMB or the study sponsor.

"An important principle in the evaluation of safety data from clinical trials is that while the data are designed to be analysed in a comprehensive fashion at the end of a trial or development program, they also must be evaluated in an ongoing fashion, so that important safety signals can be detected early and that trial participants are protected." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. Identification and Evaluation of Risk from Clinical Trial Data)

A sponsor may establish a schedule of interim analyses. The study protocol will generally describe this schedule and will also typically describe the statistical approach to the interim analysis of trial data. To minimize the potential for bias, these descriptions should be completed before the conduct of any interim analyses.

The IEC/IRB should conduct follow-up reviews in accordance with established procedures. In general, the IEC/IRB should conduct follow-up review of each ongoing trial at scheduled intervals appropriate to the degree of risk, but, generally, at least once per year.

What should be done if the benefit-risk profile of a study becomes unfavourable?

The sponsor should notify investigator(s), the IEC(s)/IRB(s), and in accordance with national/local laws and regulations, the national regulatory authority if the benefit-risk profile of a study becomes unfavourable. In consultation with the IEC(s)/IRB(s), investigator(s), and regulatory authority(ies), the sponsor may need to amend the study protocol and/or revise the investigator's brochure and informed consent document(s) to reflect the new information.

"If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor should issue a prompt notification to all parties, namely regulatory authorities, investigators and IECs/IRBs. A significant safety issue could be defined as one that has a significant impact on the course of the clinical trial or programme (including the potential for suspension of the trial programme or amendments to protocols), or warrants immediate update of informed consent." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI., *Regulatory Reporting and other Communication of Safety Information from Clinical Trials*)

What happens if the IEC/IRB determines that it must withdraw its approval/favourable opinion of the trial?

The IEC/ IRB should notify the clinical investigator and study sponsor of all decisions (favourable or unfavourable) in writing. Because a study may not proceed without approval/favourable opinion of an IEC/IRB, in some cases, it may be necessary to prematurely terminate or suspend the study (See ICH E6, Section 4.12). Should a study

be prematurely terminated, any subjects currently participating should be notified and procedures for withdrawal of enrolled subjects should consider the rights and welfare of the subjects.

In other cases, the unanticipated risk(s) might be appropriately managed through a protocol change (e.g. eliminating a study arm, introducing additional safety monitoring or testing, etc.) Note, however, that except where necessary to eliminate an immediate hazard(s) to trial subjects, the investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IEC/IRB of a protocol amendment (see ICH E6, Section 4.5).

"Ethical review committees generally have no authority to impose sanctions on researchers who violate ethical standards in the conduct of research involving humans. They may, however, withdraw ethical approval of a research project if judged necessary." (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

If the benefit-risk profile of the study changes and/or substantive protocol modifications are made, how should the information be communicated to study subjects? How is this documented?

"Sponsors and investigators have a duty to… renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate… " (CIOMS, International Ethical Guidelines, Guideline 6)

Periodically in long-term studies, the investigator should also consider renewing consent (e.g. in long-term studies involving elderly subjects).

Communicating the new information to study subjects should follow customary procedures for obtaining and documenting informed consent.

What is an Independent Data and Safety Monitoring Board (DSMB, also known as an independent Data Monitoring Committee [DMC])?

An independent data and safety monitoring board (DSMB) is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DSMB advises the sponsor regarding the continuing safety of current trial participants and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

"At intervals defined by the protocol, the DSMB reviews and evaluates the data on clinical efficacy and safety collected during the study, and assesses reports on cumulated serious adverse events (SAEs). The DSMB may also be requested by the sponsor to conduct emergency reviews of data to assess safety-related issues." "At the conclusion of the review, the DSMB provides a written recommendation to the sponsor regarding whether a protocol should be amended and/or a study should proceed based on its review of the data and the progress report submitted by the sponsor." (Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards, WHO TDR).

An important function of a DSMB "… is to protect the research subjects from previously unknown adverse reactions; another is to avoid unnecessarily prolonged exposure to an inferior therapy." (CIOMS, International Ethical Guidelines, Commentary on Guideline 11)

Should DSMBs [DMCs] be established for every study?

All clinical trials require safety monitoring but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors and investigators. DSMBs have generally been established for large, randomized multi-site studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. DSMBs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, but a DSMB is not required or recommended for most clinical stud-

ies. DSMBs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes.

"In most cases of research involving human subjects, it is unnecessary to appoint a DSMB. To ensure that research is carefully monitored for the early detection of adverse events, the sponsor or the principal investigator appoints an individual to be responsible for advising on the need to consider changing the system of monitoring for adverse events or the process of informed consent, or even to consider terminating the study." (CIOMS, International Ethical Guidelines, Commentary on Guideline 11)

"… DSMBs are of value in the following situations:

- large randomized, multi-center high morbidity/mortality trials;
- studies where data could justify early study termination or where the design or executed data accrual is complex;
- early studies of a high-risk intervention;
- studies carried out in emergency situations in which informed consent is waived;
- studies involving vulnerable populations; or,
- studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information may have raised safety concerns."

(Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. Appendix 5, *Data and Safety Monitoring Boards*)

Implementation

Sponsors, IECs/IRBs, DSMBs (if applicable), and regulators share responsibility for ongoing safety evaluations of the investigational product(s).

The **investigator** reports unanticipated problems involving risks to subjects and provides periodic progress reports at intervals ap-

propriate to the degree of risk to sponsors and IECs/IRBs in accordance with the national/local laws and regulations. The investigator provides adequate, accurate, and objective information on risks and benefits during informed consent of study subjects, and renews the consent of the subject to continue in the study, as appropriate.

The **sponsor** monitors the study and performs safety evaluations of the investigational product(s) by analysing data received from the investigator(s) and the DSMB (if one has been appointed). The sponsor also assures reporting (including expedited reporting to investigator(s), IEC(s)/IRB(s), and the regulatory authority(ies) of adverse reactions that are both serious and unexpected.

As the study progresses, the **IEC(s)/IRB(s)** conducts follow-up reviews appropriate to the degree of risk, but generally at least once per year, including review of the investigator's progress reports to determine if the benefits still outweigh the risks.

The **regulatory authority** reviews data submitted in research or marketing permits and may require modification to a protocol as a condition to its proceeding and/or may suspend or terminate a protocol based on an unacceptable benefit-risk profile in accordance with applicable laws and regulations.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Procedures (ICH E6, Section 3.3)
- Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)

For **clinical investigators**, refer to:

- Progress Reports (ICH E6, Section 4.10)
- Safety Reporting (ICH E6, Section 4.11)
- Premature Termination or Suspension of a Trial (ICH E6, Section 4.12)
- Clinical Trial Protocol and Protocol Amendment(s), General Information (ICH E6, Section 6)

Investigator's Brochure (ICH E6, Section 7)

For **sponsors**, refer to:

Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)

Notification/Submission to Regulatory Authorities (ICH E6, Section 5.10)

Adverse Drug Reaction Reporting (ICH E6, Section 5.17)

Monitoring (ICH E6, Section 5.18)

Premature Termination or Suspension of a Trial (ICH E6, Section 5.21)

Clinical Trial Protocol, General Information (ICH E6, Section 6)

Investigator's Brochure (ICH E6, Section 7)

For **regulators**, refer to:

Surveying and Evaluating Ethical Review Practices, a complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research, WHO, 2002

See also:

The Council for International Organizations of Medical Sciences (CIOMS) Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI, Geneva, 2005.

Discussion of the WHO Principles of GCP

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 5: Review by IEC/IRB

Definitions for:

Adverse Drug Reaction (ADR) (ICH E6, 1.1)

Adverse Event (AE) (ICH E6, 1.2)

Approval (in relation to Institutional Review Boards) (ICH E6, 1.5)

Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) (ICH E6, 1.25)

Independent Ethics Committee (IEC) (ICH E6, 1.27)

Informed Consent (ICH E6, 1.28)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) (ICH E6, 1.50)

Unexpected Adverse Drug Reaction (ICH E6, 1.60)

PRINCIPLE 9: INVESTIGATOR QUALIFICATIONS

Qualified and duly licensed medical personnel (i.e., physician or, when appropriate, dentist) should be responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf.

"The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment." (The Nuremberg Code)

"Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person… " (Declaration of Helsinki)

Application

Principle 9 is applied through the responsibilities of the clinical investigator to the study subject and through the sponsor's selection of qualified investigator(s). (See also GCP Principle 10, *Staff Qualifications*)

Questions and Answers

Where may information about a clinical investigator's qualifications be obtained?

The investigator's curriculum vitae or other statement of education, training and experience may provide initial information about the investigator's qualifications to provide medical care and to conduct clinical research. Other sources of information about an investigator's qualifications may include medical licensing boards, malpractice registries, and/or disciplinary bodies that may have information about the investigator's history of medical practice. References from those familiar with the investigator's clinical and/or research practice may provide useful adjunctive information.

May a non-medical person serve as a principal investigator?

"Investigator" is defined as the "person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." (ICH E6, Section 1.34)

In most clinical research, the investigator will be a physician, dentist, or (in accordance with national/local laws, regulations, and licensure provisions) equivalent medical professional.

Where permitted under national/local laws and regulations, a non-physician may serve as a principal investigator. However, implicit in this designation are: 1) that the non-physician be qualified to personally conduct or supervise the investigation; and 2) the non-physician would need to secure the services of a physician as a subinvestigator to perform those study functions requiring medical expertise. (For example, a Ph.D. pharmacologist may be listed as a principal investigator on a pharmacokinetic study with a physician subinvestigator. Another example might be a clinical psychologist principal investigator with a physician subinvestigator.)

Within GCP, what is the investigator's responsibility for the medical care of trial subjects?

The investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care during a clinical trial. This implies that (1) the investigator is able to ensure access to a reasonable standard of medical care for study subjects for medical problems arising during participation in the trial that are, or could be related, to the study intervention, and (2) the investigator or other medically qualified individuals are readily available to provide such care during the study.

"Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study.

It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study. … When prospective or actual subjects are found to have diseases unrelated to the research or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care." (CIOMS, International Ethical Guidelines, Commentary on Guideline 21)

Implementation

The **investigator** is responsible for providing, or ensuring that subjects have access to, medical care for medical problems arising during their participation in the trial that are, or could be related to the study intervention, and for following the subjects' status until the problem is resolved.

"It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed." (ICH E6, Section 4.3)

Primary responsibility for selecting qualified clinical investigators to conduct a study resides with the **sponsor**.

The **IEC(s)/IRB(s)** is responsible for ensuring that the rights and welfare of study subjects are protected. Consideration of investigator qualifications and experience and the adequacy of the site (including the supporting staff, available facilities, and emergency procedures) by the IEC/IRB will ensure that subjects have access to appropriate care for medical problems arising during participation in the trial.

National and/or local **regulatory authorities** have indirect responsibility related to clinical investigator qualifications. Regulators (1) establish licensing and practice standards for physicians and other medical personnel, (2) enforce compliance with such standards, and (3) impose disciplinary actions, as appropriate, on physicians and

other medical personnel who fail to meet such standards. Different regulatory agencies and authorities may be responsible for the oversight of clinical research vs. the licensure and oversight of medical professionals; exchange of information among regulatory agencies is encouraged in such circumstances.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Documentation (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 5.3)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)
- Medical Care of Trial Subjects (ICH E6, Section 4.3)
- Safety Reporting (ICH E6, Section 4.11)

For **sponsors**, refer to:

- Medical Expertise (ICH E6, Section 5.3)
- Investigator Selection (ICH E6, Section 5.6)
- Allocation of Duties and Functions (ICH E6, Section 5.7)
- Ethical Obligations of External Sponsors to Provide Health-Care Services (CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guideline 21)

For **regulatory authorities**, refer to:

- WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995
- GCP Compliance Monitoring Programs by Regulatory Authorities (Good Clinical Practice: Document of the Americas, PAHO, Chapter 7)
- Ethical Obligations of External Sponsors to Provide Health-Care Services (CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guideline 21)

See also:

Discussion of the WHO Principles of GCP
- GCP Principle 10: Staff Qualifications

Definitions for:
- Investigator (ICH E6, 1.34)
- Subinvestigator (ICH E6, 1.56)
- Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 10: STAFF QUALIFICATIONS

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

GCP requires that the clinical investigator is appropriately qualified by education, training, and experience to conduct the clinical trial. GCP also requires that each clinical investigator will have adequate resources available, including sufficient staff, who are also appropriately qualified by education, training, and experience, to assist him/her with the trial and ensure the safety of study subjects.

Application

Principle 10 is chiefly applied through the clinical investigator's selection of appropriate staff to assist with the conduct of the study.

Questions and Answers

What does it mean to be "qualified" to conduct clinical research and how is this implemented within GCP?

GCP requires generally that individuals who conduct research have appropriate education, training, and experience to assume responsibility for the conduct of the trial. The investigator should have knowledge of applicable laws and regulations and broad knowledge of internationally accepted principles and practices for the conduct of clinical research within GCP, including ethical requirements for the protection of human subjects involved in the research. The investigator should also have training or expertise appropriate to carry out the requirements of the specific study protocol.

The investigator should understand and be qualified to execute the responsibility to personally supervise any individual to whom a study task is delegated. The investigator should further ensure that any individual to whom a study task is delegated is qualified by education, training, and experience to perform the delegated task, for example

that the assigned task falls within the scope of the individual's professional license(s).When delegating tasks, the investigator should consider, among other things, whether the tasks require formal medical training and whether national or local licensing requirements apply to such duties. (Duties that warrant such consideration, include, but are not necessarily limited to, the following: screening evaluations, including medical histories and assessment of inclusion/exclusion criteria; physical examinations; assessment of adverse events; assessments of primary study endpoints (e.g., tumor response, global assessment scales); control of investigational products.)

The investigator should ensure that staff are (1) familiar with the study protocol and investigational product; (2) appropriately trained to carry out trial-related duties; (3) informed/aware of their obligations to protect the rights, safety and welfare of the study subjects; and (4) informed of any requirements imposed by the national regulatory authority for GCP and the conduct of clinical studies.

What does it mean to be qualified by "education, training, and experience"; that is, what does each of these terms embrace?

Education refers to degrees, certification, and/or licensing earned as a result of formal schooling or courses of study at an institution of higher learning (e.g., M.D., Ph.D., R.N., board certification in a specified field, medical licenses). Training generally refers to short, focused programs on specific topics (e.g., a two-week training program in research ethics, an online course on GCP, "investigator training" provided by the study sponsor related to a specific protocol) and/or mentoring by an appropriately educated, trained, and experienced professional. Experience includes direct participation in activities that provide additional expertise in a specific area (e.g., various positions a physician has held during his/her practice of medicine, previous work assisting another investigator in conducting clinical research, experience as an investigator in a previous study).

Where may information about the qualifications of an investigator or the investigator's staff be obtained?

A curriculum vitae or other statement of education, training, and experience for each staff member may provide initial information about the staff member's qualifications. Other sources of information may include medical licensing boards, malpractice registries, and/or disciplinary bodies. References from those familiar with the individual's past clinical and/or research experience may provide useful adjunctive information.

How should an investigator inform a sponsor about the individuals to whom duties have been delegated?

Maintaining a list of individuals to whom the investigator has assigned each trial-related duty may assist the sponsor and regulators alike in determining which staff members were authorized to carry out specific duties during the course of the trial.

Implementation

The **investigator** bears primary responsibility for (1) selecting qualified staff to assist in the conduct of the investigation; (2) ensuring that study staff receive appropriate training, related to ethics and consent procedures as well as requirements of the specific protocol; (3) establishing clear procedures for activities related to the conduct of the study; (4) assigning tasks to staff, based on their qualifications, experience, and professional licenses; and (5) personally supervising staff to ensure that they satisfactorily fulfill their study-related duties. Although the investigator may delegate tasks to members of his/her staff, nevertheless, the investigator retains overall responsibility for the study and ensuring that his/her staff complies with applicable laws and regulations for human subject protection and the conduct of clinical research.

The **IEC/IRB** is responsible for ensuring that the rights and welfare of study subjects are protected. Consideration of the site's characteristics (e.g., number and qualifications of supporting staff, available

facilities and equipment, and emergency procedures) will allow the IEC/IRB to evaluate the adequacy of the site, and ensure that subjects' welfare is not compromised during the trial.

Sponsors have the responsibility for selecting appropriately qualified investigators to conduct the study; part of that consideration is ensuring that investigators have sufficient staff (also with appropriate qualifications) available, who are appropriately trained to conduct all study-related activities, and who understand how to capture and document required observations and data.

In accordance with national and/or local laws and regulations, **regulatory authorities** may inspect study sites to determine if the conduct of the study is in compliance with local laws/regulations. Such inspections would include finding out who was assigned responsibility for conducting various study-related activities (e.g., screening subjects to determine if they meet inclusion/exclusion criteria; obtaining informed consent; conducting physical examinations; collecting and analysing study data; recording, transcribing, or reporting data to the sponsor; administering the investigational product to subjects), and determining whether these activities were appropriately assigned and within the scope of the staff member's professional license(s).

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Elements of the Review (WHO Operational Guidelines for Ethics-Committees that Review Biomedical Research, Section 6.2)

For **clinical investigators**, refer to:

Investigator's Qualifications and Agreements (ICH E6, Section 4.1)
Adequate Resources (ICH E6, Section 4.2)
Investigational Product(s) (ICH E6, Section 4.6)

For **sponsors**, refer to:

Medical Expertise (ICH E6, Section 5.3)
Trial Design (ICH E6, Section 5.4)
Trial Management, Data Handling, Recordkeeping, and Independent Monitoring Committee (ICH E6, Section 5.5)

Investigator Selection (ICH E6, Section 5.6)
Allocation of Duties and Functions (ICH E6, Section 5.7)

For **regulatory authorities**, refer to
Conducting the Inspection (A Guide to Clinical Investigator Inspections, PAHO, Annex 4, Section 2)

See also:

Discussion of the WHO Principles of GCP
GCP Principle 9: Investigator Qualifications

Definitions for:
Investigator (ICH E6, 1.34)
Subinvestigator (ICH E6, 1.56)
Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 11: RECORDS

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Principle 11 embraces the concepts of data quality and data integrity as well as appropriate procedures for data handling and record-keeping. Also implicit in this principle is the preparation and maintenance of essential documents: i.e., documents (including source documents) that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

Application

Principle 11 is applied through: 1) the understanding and application of basic elements of data quality and integrity; 2) adherence to the study protocol as well as applicable written procedures for collecting, recording, reporting, maintaining and analysing clinical trial information; and 3) the preparation of essential documents (including source documents), at all stages throughout the conduct of the clinical trial.

Questions and Answers

What is "clinical trial information"? What is meant by "essential documents"?

The term, "clinical trial information," encompasses all study related data, materials, and documents. The term includes "[a]ll records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken." (ICH E6, 1.22)

Essential documents are "… those documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements." Essen-

tial documents are "… usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of the data collected." (ICH E6, Section 8)

Examples include:

- Source data: "All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)." (ICH E6, 1.51)
- Source documents: "Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)." (ICH E6, 1.52)
- Case report forms: "… [P]rinted, optical, or electronic document[s] designed to record all of the protocol-required information to be reported to the sponsor on each trial subject." (ICH E6, 1.11)
- Correspondence between any of the parties who conduct or oversee the research (e.g. approval/favourable decision by the IEC/IRB; reports of adverse events submitted to the sponsors, IECs/IRBs, and regulators; monitor's reports to the sponsor)
- Other study related documents and materials (e.g. study protocol, protocol amendments, investigator's brochure, clinical investigator's curriculum vitae, approved consent form, subjects' signed consent forms, subject screening logs, documentation of investigational product destruction, advertisements used to recruit subjects, reports by independent data monitoring committees)

What is meant by "recording"?

"Recording" is the act of writing down or otherwise committing to durable medium (e.g., paper, electronic medium, etc.) information or data to provide evidence of what has occurred or has been observed. All of the parties who conduct or oversee clinical trials are responsible for preparing records (i.e. "essential documents") that document their activities and data or observations related to the trial.

What is meant by "data quality"? What is meant by "data integrity"? How are the terms related, and how are data quality and integrity achieved within GCP?

"Data quality" refers to the essential characteristics of each piece of data; in particular, quality data should be:

- accurate
- legible
- complete and contemporaneous (recorded at the time the activity occurs)
- original
- attributable to the person who generated the data.

"Data integrity" refers to the soundness of the body of data as a whole. In particular, the body of data should be credible, internally consistent, and verifiable.

Quality and integrity are both essential for data to be relied upon for regulatory decision-making. Data quality and integrity are achieved when each piece of data is collected in accordance with the study protocol and procedures, giving attention to each of the quality characteristics above, and subsequently handled (e.g. transcribed, analysed, interpreted, reported) so that the quality characteristics of the original data (i.e. accuracy, legibility, completeness, etc.) are preserved.

What is meant by "handling"? How are "quality and integrity" preserved as data and documents are "handled"?

Handling refers to how data are maintained, analysed, interpreted, and shared, transmitted, or reported to others. For example, source data are often transcribed by the investigator into a case report form (CRF), which in turn is submitted to the sponsor for further handling.

Establishing SOPs to identify the various steps in data handling (at both investigator and sponsor sites) and to articulate the associated roles and responsibilities of investigator and sponsor staff may help preserve quality and integrity as data is handled.

Study monitoring also helps to ensure that data quality and integrity are preserved throughout the study by, for example, verifying that data transmitted to the sponsor in the CRF accurately reflect information about the study subject that was recorded in the medical records or case histories.

"Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes and corrections. ... Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections." (ICH E6, Section 4.9)

Who must keep clinical trial information and for how long? What is meant by the term "storage"?

All of the parties who conduct or oversee research involving human subjects are expected to keep records and materials related to their specific trial responsibilities and activities for the period of time required by national/local laws and regulations, or if such laws do not exist, in accordance with GCP standards.

Within GCP, generally, "[e]ssential documents should be retained until at least 2 years after the last approval of a marketing applica-

tion… and until there are no pending or contemplated marketing applications… or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor." (ICH E6, Section 4.9)

"Storage" (or "archiving") implies that records are appropriately stored for future use, for example, to ensure their preservation and to enable direct access to the records when required by the sponsor, IEC/IRB, monitor or regulatory authorities. "The investigator/institution should take measures to prevent accidental or premature destruction of these records." (ICH E6, Section 4.9)

Why is it necessary for IECs/IRBs, investigators, sponsors, and monitors to maintain clinical trial information?

Clinical trial information should be maintained to allow accurate reconstruction and evaluation of the trial's conduct and verification of the trial's results.

How do investigators know which records should be maintained and the methods for maintaining them?

The study protocol generally specifies the information to be captured and the methods to be used (e.g., by providing "[s]amples of the standardized case-report forms to be used… ," describing "… the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, if applicable, the measures proposed to determine the extent of compliance of subjects with the treatment… ," "[m]ethods of recording and reporting adverse events or reactions…" (CIOMS, International Ethical Guidelines, Appendix 1).

Record-keeping and retention requirements may also be specified by national or local law and regulations.

What is meant by "reporting"? How are essential documents and data combined to report the outcome of the trial?

Reporting is the act of providing information or data to another party. National laws and regulations may require certain information to be reported within specific time frames, for example, reports of serious unanticipated adverse events.

Responsibility for reporting clinical trial information and results is shared by:

- the study sponsor, who reports adverse events to regulators, and prepares summary reports about clinical studies for inclusion in applications to obtain research permits or to market an investigational product;
- the monitor, who prepares and submits written reports of monitoring visits and trial-related communications to the sponsor;
- the clinical investigator who submits, for example, case report forms (CRFs) to the sponsor; progress reports or written summaries of the trial's status to the institution, the IEC/IRB, and the sponsor; safety reports (e.g., adverse event reports, laboratory anomalies) to the sponsor and IEC/IRB; final reports upon completion of the trial to the sponsor, IEC/IRB, and regulatory authorities;
- the IEC/IRB, which notifies the investigator and institution, and sometimes the regulatory authority(ies) about trial-related decisions and opinions (e.g., decisions to suspend or terminate a study), the reasons for such decisions/opinions, and procedures for appealing them.

"The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF, which are derived from source documents should be consistent with the source documents or the discrepancies should be explained." (ICH E6, Section 4.9; see also, ICH E6, Section 4.10: Progress Reports; ICH E6, Section 4.11: Safety Reporting, and ICH E6, Section 4.13: Final Report(s) by Investigator/Institution.)

What is meant by "interpretation" of clinical trial information and how is this achieved within GCP?

"Interpreting" clinical trial information refers to analysing the meaning and significance of data and other observations and information collected during the clinical trial. The study protocol generally describes the overall plan for interpreting clinical trial data. Sponsors, in close collaboration with the investigator(s), generally analyse and interpret clinical trial data and prepare summaries as part of an application for approval to market an investigational product. Such summaries and analyses enable regulators to make a determination about the safety and/or effectiveness of a product that is the subject of a research permit or marketing application.

The sponsor

- "… should utilize appropriately qualified individuals" [e.g., biostatisticians, clinical pharmacologists and physicians, as appropriate] "to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports." (ICH E6, Section 5.5)
- should include in the study protocol a "… description of the statistical methods to be employed, including timing of any planned interim analysis(ses), … the level of significance to be used, … procedure for accounting for missing, unused, and spurious data, procedures for reporting any deviations from the original statistical plan… selection of subjects to be included in the analyses… " (ICH E6, Section 6.9)

How should clinical trial results be publicly reported?

"Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. … Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication." (Declaration of Helsinki)

The study protocol may include:

- "[i]n the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or by reporting to the drug registration authority." (CIOMS International Ethical Guidelines, Appendix 1)
- "[c]ircumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people." (CIOMS International Ethical Guidelines, Appendix 1)

Who should have access to clinical trial records?

Sponsors, monitors, IECs/IRBs, and regulators generally require direct access to all information pertaining to the conduct and oversight of the clinical trial. Direct access means that these parties have "[p]ermission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial." (ICH E6, 1.21)

"Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies)." (ICH E6, Section 8)

Note that consent forms should inform study subjects "[t]hat the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access." (ICH E6, 4.8) (See also GCP Principle 7: *Informed Consent*)

In addition, sponsors, monitors, investigators and regulators should be aware of the need to handle clinical trial information in a manner

that protects the privacy and confidentiality of trial subjects. These parties should also be fully informed about national/local laws/ regulations related to privacy and confidentiality. (See also GCP Principle 12: *Confidentiality/Privacy*)

Implementation

IECs/IRBs, investigators, sponsors, and regulators all bear responsibility for documenting their activities within GCP, and maintaining records pertaining to duties related to the conduct or oversight of the clinical trial for the time required under national or local law and regulations. All parties are responsible for ensuring the accuracy, completeness, legibility and availability (as necessary) of such documents.

IECs/IRBs document their reviews of study protocols and informed consent/recruitment/ advertising materials through minutes that capture the IECs'/IRBs' deliberations and through copies of correspondence with the clinical investigator.

Investigators prepare and maintain case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

Sponsors ensure that study protocols address appropriate data handling and record-keeping requirements and design CRFs appropriately to facilitate the capture of all significant trial-related data and observations. Sponsors also secure the services of monitors to ensure compliance of the clinical investigators, and verify that the study was carried out according to the approved study protocol.

Regulators rely on clinical trial information to support regulatory decision-making and may inspect all of the parties involved in conducting or overseeing research. Critical to regulatory inspection is direct access to and review of existing clinical trial records. As part of an inspection, regulators compare records at the clinical investigator site and sponsor site with data and reports submitted to the regulatory authority to verify the information submitted. Regulators also prepare and maintain records of their inspections and findings.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Procedures (ICH E6, Section 3.3)
- Records (ICH E6, Section 3.4)
- Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)
- Documentation and Archiving (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 10)

For **clinical investigators**, refer to:

- Communication with IRB/IEC (ICH E6, Section 4.4)
- Compliance with Protocol (ICH E6, Section 4.5)
- Records and Reports (ICH E6, Section 4.9)
- Progress Reports (ICH E6, Section 4.10)
- Safety Reporting (ICH E6, Section 4.11)
- Final Report(s) by Investigator/Institution (ICH E6, Section 4.13)
- Clinical Trial Protocol and Protocol, General Information (ICH E6, Section 6)
- Essential Documents for the Conduct of a Clinical Trial (ICH E6, Section 8)

For **sponsors**, refer to:

- Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)
- Record Access (ICH E6, Section 5.15)
- Adverse Drug Reaction Reporting (ICH E6, Section 5.17)
- Monitoring (ICH E6, Section 5.18)
- Audit (ICH E6, Section 5.19)
- Clinical Trial/Study Reports (ICH E6, Section 5.22)
- Clinical Trial Protocol and Protocol (ICH E6, Section 6)
- Essential Documents for the Conduct of a Clinical Trial (ICH E6, Section 8)
- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)

Guidance on Data Elements for Transmission of Individual Case Safety Reports (ICH E2B)
Statistical Principles for Clinical Trials (ICH E9)

For **regulatory authorities**, refer to:

A Guide to Clinical Investigator Inspections (Good Clinical Practices: Document of the Americas, PAHO, Annex 4)
GCP Compliance Monitoring Programs by Regulatory Authorities (Chapter 7, Good Clinical Practices: Document of the Americas, PAHO)
Surveying and Evaluating Ethical Review Practices (WHO Operational Guidelines,)
Statistical Principles for Clinical Trials (ICH E9)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 2: Protocol
GCP Principle 6: Protocol Compliance
GCP Principle 7: Informed Consent
GCP Principle 12: Confidentiality/Privacy
GCP Principle 14: Quality Systems

Definitions for:

Case Report Form (ICH E6, 1.11)
Clinical Trial/Study Report (ICH E6, 1.13)
Compliance (in relation to trials) (ICH E6, 1.15)
Direct Access (ICH E6, 1.21)
Documentation (ICH E6, 1.22)
Essential Documents (ICH E6, 1.23)
Interim Clinical Trial/Study Report (ICH E6, 1.32)
Monitoring (ICH E6, 1.38)
Monitoring Report (ICH E6, 1.39)
Original Medical Record (ICH E6, 1.43)
Protocol (ICH E6, 1.44)
Source Data (ICH E6, 1.51)
Source Documents (ICH E6, 1.52)
Standard Operating Procedures (SOPs) (ICH E6, 1.55)

PRINCIPLE 12: CONFIDENTIALITY/PRIVACY

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

"The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject." (Declaration of Helsinki)

"The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality." (CIOMS, International Ethical Guidelines, Guideline 18)

Application

Principle 12 is applied (1) through appropriate procedures to protect the privacy of the subject, and (2) by document and data control to protect the confidentiality of the subject's information.

Principle 12 is also applied through the informed consent process which requires as an essential element that certain explanations be provided to the subject about the confidentiality of the subject's records and about access to those records by monitor(s), auditor(s), the IEC/IRB, and the regulatory authority(-ies).

Questions and Answers

What is meant by "privacy"? What is meant by "confidentiality"?

Privacy embraces the concept that each individual should have the right to control personal and sensitive information about him/her. Privacy implies that such information, which may be contained in medi-

cal records, personal diaries, or elsewhere, will be protected and not disclosed without the knowledge/permission of the individual to whom it pertains.

Privacy may not be absolute, however. For example, some information, such as exposure to a communicable disease, may be subject to limited disclosure under public health laws; access to information contained in clinical study records may be required by regulators to verify data submitted in a marketing application. Thus, individuals who participate in clinical trials should be told the extent to which their information will be protected and the circumstances under which the information will be disclosed, to whom, and the purpose(s) for doing so.

Confidentiality embraces the concept that parties who obtain private information from patients and subjects will (1) protect the information itself and any records that contain such information from deliberate or accidental disclosure; (2) develop and follow procedures for release of the information only to authorized parties who have a legitimate need for it, including notification of the patient/subject prior to any disclosure.

Who is responsible for protecting the confidentiality of the subjects' private information?

At all times throughout the investigation, all parties (sponsor, monitor, IEC/IRB, investigator, investigator's staff, and regulators) should protect subjects' private information and ensure that all data are secured against unauthorized access. This applies but is not limited to subjects' case report forms (CRFs), source data, source documents, and safety reports.

"It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject." (Declaration of Helsinki)

How is confidentiality implemented within GCP?

"… Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means." (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

Other mechanisms to protect information include, but are not limited to:

- coding or encryption of data;
- restricting access to study records and subjects' medical files (e.g., passwords on electronic files, files secured in locked cabinets or secured storage areas);
- maintaining subjects' names and identifying information separately from case report forms;
- establishing and following procedures to ensure subjects' private information and trial data are protected.

Why should potential risks related to release of private information be disclosed to study subjects?

Each subject needs to consider whether risks related to release of private information are sufficiently controlled, such that he/she is still willing to participate in the investigation.

"Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress." (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

"Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. Drug regulatory authorities have the right to inspect clini-

cal-trial records, and a sponsor's clinical-compliance audit staff may require and obtain access to confidential data. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects." (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

How should subjects be informed of the measures that will be used to protect their private information? How should potential risks related to release of private information be disclosed to study subjects?

The informed consent document should describe (1) who will have access to personal data of the research participants, including medical records and biological samples; (2) the measures taken to ensure the confidentiality and security of research participants' personal information; and (3) the potential risks to subjects if such measures are breached (e.g., stigma, loss of reputation, potential loss of insurability, etc.).

"… During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality." (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

"Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:...

> "(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access."
>
> "(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regula-

tions, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential." (ICH E6, Section 4.8)

"The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection." (ICH E6, Section 5.15)

Implementation

IECs/IRBs review/approve the informed consent procedures and document to ensure, among other things, that there is adequate explanation regarding (1) the risks related to release of the subject's private information, (2) how the confidentiality of the subject's records will be maintained, and (3) persons who may have access to the subject's records (e.g., monitor(s), auditor(s), the IEC/IRB, and the regulatory authority(-ies)).

Investigators should (1) implement procedures to protect and restrict access to study records and private information (e.g., password protection for files, keeping study records in secured areas), (2) follow national/local laws and regulations relating to privacy and confidentiality, (3) ensure that study staff are aware of and receive appropriate training related to their responsibility and procedures to be used for protecting subjects' private information and records, (4) ensure that study staff follow the procedures established for this purpose, and (5) ensure that the consent form and process inform study subjects about the procedures to be used to protect their private information and the circumstances under which their medical and study records may be viewed by regulators, sponsors, monitors, and/or the IEC/IRB.

Sponsors ensure that sites (1) allow regulators, IECs/IRBs, and monitors direct access to records necessary to verify compliance with national/local laws and regulations pertaining to the conduct of clinical trials, and (2) inform subjects about, and obtain their consent for, such access.

Regulatory authorities need to (1) be alert to issues of subject confidentiality, and (2) review sponsors', clinical investigators', and IECs'/IRBs' compliance with applicable national/local laws and regulations for handling private information and informing subjects about these issues.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Elements of the Review, Protection of Research Participant Confidentiality (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2.4)

For **clinical investigators**, refer to:

- Informed Consent of Trial Subjects (ICH E6, Section 4.8)
- Safety Reporting (ICH E6, Section 4.11)

For **sponsors**, refer to:

- Trial Management, Data Handling, Recordkeeping, and Independent Monitoring Committee (ICH E6, Section 5.5)
- Record Access (ICH E6, Section 5.15)
- Monitoring (ICH E6, Section 5.18)
- Clinical Trial Protocol and Protocol Amendments, Direct Access to Source Data/Documents (ICH E6, Section 6.10)

For **regulatory authorities**, refer to:

- Confidentiality in the Survey and Evaluation Processes (Surveying and Evaluating Ethical Review Practices, a complementary guideline to the Operational Guidelines for Ethics Committees the Review Biomedical Research, WHO, 2002), Section 8
- Safeguarding Confidentiality (Guideline 18, CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva 2002)

See also:

Discussion of WHO GCP Principles
- GCP Principle 2: Protocol
- GCP Principle 3: Risk Identification
- GCP Principle 4: Benefit-Risk Assessment
- GCP Principle 7: Informed Consent
- GCP Principle 11: Records

Definitions for:
- Audit (ICH E6, 1.6)
- Confidentiality (ICH E6, 1.16)
- Direct Access (ICH E6, 1.21)
- Inspection (ICH E6, 1.29)
- Original Medical Record (ICH E6, 1.43)
- Subject Identification Code (ICH E6, 1.58)
- Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 13: GOOD MANUFACTURING PRACTICE

Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.

"The sponsor should ensure that the investigational product(s) … is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable… " (ICH E6, Section 5.13)

Application

Principle 13 is applied through 1) appropriately characterizing the investigational product (including any active comparator(s) and placebo, if applicable), 2) adhering to applicable Good Manufacturing Practice (GMP) standards in the manufacturing, handling and storage of the investigational product, and 3) using the product according to the approved study protocol.

Questions and Answers

What is meant by "applicable" Good Manufacturing Practice" (GMP)?

"Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards." "…GMP covers all aspects of production, from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process – every time the product is made." "…WHO has established detailed guidelines for good manufacturing practice. Many countries have formulated their own requirements for GMP based on

WHO GMP." (WHO, *Good Manufacturing Practice in Pharmaceutical Production*)

Compliance with GMP standards is intended to:

- assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials;
- assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product;
- protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilization, contamination and cross-contamination, mix-ups, incorrect labeling, etc.), or from starting materials and components of inadequate quality; and
- document all changes in the manufacturing process.

"...[T]he principles of GMP should be applied, as appropriate, to the preparation of [investigational] products." (WHO, *Good Manufacturing Practice in Pharmaceutical Production*)

In accordance with national/local laws and regulations, GMP compliance may be a requirement. Where not required by national/local laws and regulations, GMP standards provide important guidance to the manufacture of quality investigational products.

What constitutes handling and storage of the investigational product(s)?

In addition to packaging, labeling, quarantine and release associated with the manufacturing process at the production site, handling of the product by the sponsor also includes shipping, return, and final disposition of the investigational products.

"Investigational products should be shipped in accordance with the orders given by the sponsor. A shipment is sent to an investigator only after the following two-step release procedure: (i) the release of the product after quality control ("technical green light"); and (ii) the

authorization to use the product, given by the sponsor ("regulatory green light"). Both releases should be recorded. The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol. A detailed inventory of the shipments made by the manufacturer should be maintained, and should make particular mention of the addressee's identification. Returned investigational products should be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products should be kept."(WHO, *Good Manufacturing Practice in Pharmaceutical Production*)

With respect to storage, "[t]he sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations." (ICH E6, Section 5.13)

"The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof..." (ICH E6, Section 5.14)

At the site, the investigator is responsible for ensuring that the investigational product(s) are "… stored as specified by the sponsor ... and in accordance with applicable regulatory requirements" … [and] "are used only in accordance with the approved protocol." (ICH E6, Section 4.6)

Implementation

Responsibility for implementing this principle is shared by sponsors (or contract manufacturers/ contract research organizations), investigators, and regulators.

Sponsors implement this principle directly or indirectly through contract, by developing and characterizing the investigational product.

They make the necessary notifications/submissions to the applicable regulatory authority(ies), identify GMP requirements, if any, that may apply to the manufacturing, handling and storage of the investigational product, and ensure compliance with those requirements. Sponsors manufacture the investigational product directly or have it manufactured under contract at a manufacturing site in accordance with applicable GMP. They are responsible within GCP for the handling, storage, distribution and final disposition of the investigational product(s).

The sponsor also develops the study protocol and investigator's brochure, monitors protocol compliance, and ensures that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational products for the trial and documentation thereof.

Investigators are responsible for familiarity with the investigator's brochure and for conducting the research in compliance with the protocol, including any instructions for storing and handling investigational products. Investigators are responsible for explaining correct use (including handling and storage) of the investigational product to the study subjects. Investigators also ensure that any unused investigational products are returned to the sponsor after the trial is completed.

In accordance with national/local laws and regulations, **regulators** may establish GMP requirements for investigational products, review manufacturing data submitted in support of research permits or marketing applications, and/or inspect manufacturing facilities. Because investigational products may be imported, regulators should be familiar with the manufacturing requirements in the country of origin and their conformance with international GMP standards.

Regulators may also inspect investigators for compliance with the study protocol, including instructions for storing and handling investigational products.

For more information (including Roles and Responsibilities)

For guidelines on Good Manufacturing Practices and Inspection, refer to:

- WHO, *A Compendium of Guidelines and Related Materials, Volume 2: Good Manufacturing Practices and Inspections* (http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpthree_inves.html)
- Active Pharmaceutical Ingredients for Use in Clinical Trials (GMP for Active Pharmaceutical Ingredients, ICH Q7A, Section XIX)

For **clinical investigators**, refer to:

- Compliance with Protocol (ICH E6, Section 4.5)
- Investigational Product(s) (ICH E6, Section 4.6)

For **sponsors**, refer to:

- Manufacturing, Packaging, Labeling, and Coding Investigational Products (ICH E6, Section 5.13)
- Supplying and Handling Investigational Product(s) (ICH E6, Section 5.14)
- Monitoring (ICH E6, Section 5.18)
- Noncompliance (ICH E6, Section 5.20)

For **regulatory authorities**, refer to:

- WHO, *A Compendium of Guidelines and Related Materials, Volume 2: Good Manufacturing Practices and Inspections* (http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpthree_inves.html)
- Active Pharmaceutical Ingredients for Use in Clinical Trials (GMP for Active Pharmaceutical Ingredients, ICH Q7A, Section XIX)

See also:

Discussion of the WHO Principles of GCP:

- GCP Principle 6: Protocol Compliance

Definitions for:

- Comparator (Product) (ICH E6, 1.14)
- Compliance (in relation to trials) (ICH E6, 1.15)
- Contract Research Organization (CRO) (ICH E6, 1.20)
- Investigational Product (ICH E6, 1.33)
- Monitoring (ICH E6, 1.38)

PRINCIPLE 14: QUALITY SYSTEMS

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Application

Principle 14 is applied through development of procedures to control, assure, and improve the quality of data and records and the quality and effectiveness of processes and activities related to the conduct and oversight of clinical research.

Questions and Answers

What is meant by "quality" in the context of a clinical trial?

"Quality" is a measure of the ability of a product, process, or service to satisfy stated or implied needs. A high quality product readily meets those needs.

In the context of a clinical trial, quality may apply to data (e.g., data are accurate and reliable) or processes (e.g., compliance with the study protocol and GCP; ensuring informed consent; adequate data handling and record-keeping, etc.). (See WHO GCP Principles 6: *Protocol Compliance*; 7: *Informed Consent*; 11: *Records*)

A common way to assure data and process quality is through the development and application of standard operating procedures (SOPs) that define responsibilities, specify records to be established and maintained, and specify methods and procedures to be used in carrying out study-related activities. SOPs coupled with close personal supervision of the trial's conduct by the clinical investigator and careful monitoring by the sponsor help to ensure that processes are consistently followed and activities are consistently documented. As a result, data collected using such procedures and under such supervision should ordinarily be reliable enough for regulatory decision-making.

What are "quality systems" with respect to clinical trials?

"Quality systems" for clinical trials are formalized practices (e.g., monitoring programs, auditing programs, complaint handling systems) for periodically reviewing the adequacy of clinical trial activities and practices, and for revising such practices as needed so that data and process quality are maintained.

How are quality systems implemented within GCP?

Within GCP, quality systems are implemented through quality management: that is, through coordination of activities by the sponsor, by the investigator(s) and site staff, by the IEC(s)/IRB(s) and by regulators to direct and control their operations with respect to quality. Quality management embraces three major components: quality control; quality assurance; and quality improvement.

What is the distinction between "quality control", "quality assurance", and "quality improvement"?

"Quality control" means the steps taken during the generation of a product or service to ensure product/service quality. For a clinical trial, "quality control" encompasses steps taken during the clinical trial (e.g., investigator supervision, sponsor monitoring, and any ongoing review by regulatory authorities) to ensure that the trial meets protocol and procedural requirements and is reproducible.

"Quality assurance" refers to a systematic process to determine whether the quality control system is working and effective. Most often, quality assurance in clinical trials is implemented by the sponsor through independent auditing of quality control activities and, where applicable, by regulatory authorities through inspection of quality control systems and activities. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion.

"The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to

evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements." (ICH E6, Section 5.19)

"Quality improvement" refers to a systematic process for taking the knowledge gained through quality assurance audits and activities and using this knowledge to make changes in systems and activities in order to increase the ability to fulfill quality requirements then and for the future.

What is study monitoring?

Monitoring is "[t]he act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s)." (ICH E6, 1.38; see also ICH E6 Section 5.18, generally, for detailed guidance on study monitoring.)

What is the difference between monitoring, auditing, and inspecting?

Monitoring is a quality control activity conducted by the sponsor or a representative of the sponsor to ensure that the research is conducted in accordance with the study protocol, GCP, and applicable regulatory requirements and that research data are accurate, complete, and verifiable from source documents. Monitors generally compare source documents with case report forms and seek to resolve any discrepancies. Monitors also try to verify that activities related to protecting the rights and welfare of study subjects (e.g., prior approval of the IEC/IRB, obtaining legally effective informed consent from all study subjects) were appropriately carried out.

Auditing is an independent quality assurance activity used by the sponsor to evaluate the effectiveness of a monitoring program and/or specific monitoring activities. Auditing is distinguished from monitoring by the fact that monitoring is carried out while the study is in progress (see discussion of "Quality control" above) whereas auditing can occur anytime during or after the study.

An inspection is "[t]he act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities or at other establishments deemed appropriate by the regulatory authority(ies)." (ICH E6, 1.29) The purpose of such inspection is to determine whether research was conducted in compliance with national/local laws and regulations for the conduct of research and the protection of human subjects.

Implementation

All of the parties who conduct and oversee clinical trials (sponsors, clinical investigators, IECs/IRBs, and regulatory authorities) should adopt and implement quality systems for the processes and activities for which they are responsible.

Sponsors secure the services of monitors to ensure compliance of the clinical investigators and verify that the study was carried out according to the approved study protocol. Sponsors also audit the monitors' performance and other quality control activities and systems to ensure each system's performance.

Monitors review study records at the sites, report their findings to the sponsor, and prepare written reports that document each site visit or trial-related communication.

Investigators supervise to ensure that study staff follow established procedures for the conduct of the study, e.g. obtaining IEC/IRB approval of the study, obtaining informed consent from subjects, establishing and maintaining subjects' case histories, transcribing data from subjects' medical files to the CRFs, reporting adverse events and other unanticipated problems, etc.

IECs/IRBs develop and adopt SOPs for reviewing studies and informing the clinical investigator of any required modifications to the study protocol, and for assuring that such modifications are in place before

the study proceeds. In accordance with national/local laws and regulations, IECs/IRBs may develop SOPs to allow IEC/IRB members or a third party to observe the consent process to verify that subjects are being provided the opportunity to ask questions about the study and that subjects receive a copy of the informed consent document. IECs/IRBs implement systems to assure that continuing review of the study takes place at intervals appropriate to the degree of risk, and that investigators are notified so that they may provide the necessary documentation to the IEC/IRB in advance of the deadline.

In accordance with applicable laws/regulations, **regulators** may inspect all parties that conduct or oversee research and verify the information submitted to the regulatory authority. Regulators may ask for sponsors' monitoring plans as a condition of allowing a study to proceed. Regulatory authorities also optimally develop SOPs and quality systems for internal regulatory activities, including policies and procedures for reviewing product applications and for the conduct of GCP inspections.

For more information (including Roles and Responsibilities)

For **sponsors**, refer to:

- Quality Assurance and Quality Control (ICH E6, Section 5.1)
- Trial Management, Data Handing, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)
- Monitoring (ICH E6, Section 5.18)
- Audit (ICH E6, Section 5.19)
- Noncompliance (ICH E6, Section 5.20)
- Monitoring Arrangements (Clinical investigation of medical devices for human subjects, Part 2: Clinical investigation plans, International Standards Organization (ISO), 14155-2, 4.34)

For **monitors**, refer to:

- Monitoring (ICH E6, Section 5.18)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)

For **IECs/IRBs**, refer to:

- Composition, Functions, and Operations (ICH E6, Section 3.2)
- Procedures (ICH E6, Section 3.3)
- WHO Surveying and Evaluating Ethical Review Practices: A complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research.

For **regulatory authorities**, refer to:

- Noncompliance (ICH E6, Section 5.20)
- GCP Compliance Monitoring Programs by Regulatory Authorities (Chapter 7, Good Clinical Practices: Document of the Americas, PAHO)
- A Guide to Clinical Investigator Inspections (Annex 4, Good Clinical Practices: Document of the Americas, PAHO)
- Optional Guideline for Good Clinical Practice Compliance and Quality Systems Auditing (European Network of GCP Auditors and other GCP Experts [ENGAGE], European Forum for Good Clinical Practice, August 1997)

See also:

Discussion of the WHO Principles of GCP

- GCP Principle 2: Protocol
- GCP Principle 6: Protocol Compliance
- GCP Principle 11: Records

Definitions for:

- Audit (ICH E6, 1.6)
- Audit certificate (ICH E6, 1.7)
- Audit report (ICH E6, 1.8)
- Audit trail (ICH E6, 1.9)
- Compliance (in relation to trials) (ICH E6, 1.15)
- Direct Access (ICH E6, 1.21)
- Monitoring (ICH E6, 1.38)
- Monitoring Report (ICH E6, 1.39)
- Quality Assurance (QA) (ICH E6, 1.46)
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United States of America
Good clinical practice in FDA regulated clinical trials.
http://www.fda.gov/oc/gcp/default.htm

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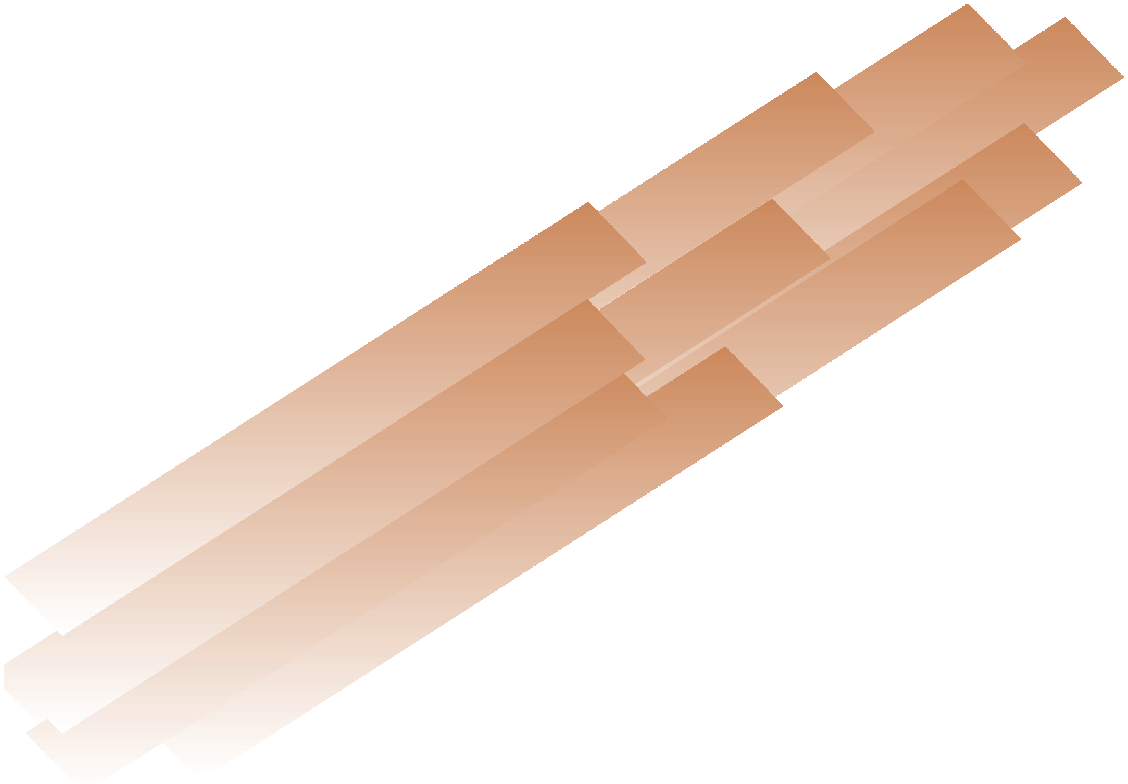
Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance



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GUIDANCE FOR INDUSTRY[1]

E6 Good Clinical Practice: Consolidated Guidance

INTRODUCTION

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guidance was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guidance should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guidance may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 Adverse drug reaction (ADR): In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal

[1] This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, April 1996. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the United States. This guidance was published in the *Federal Register* on May 9, 1997 (62 FR 25692), and is applicable to drug and biological products. This guidance represents the Agency's current thinking on good clinical practices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse event (AE): An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol): See Protocol Amendment.

1.4 Applicable regulatory requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where trial is conducted.

1.5 Approval (in relation to institutional review boards (IRBs)): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

1.6 Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit certificate: A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit report: A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit trail: Documentation that allows reconstruction of the course of events.

1.10 Blinding/masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s)

being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case report form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

1.12 Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guidance for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials): Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee: A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

1.19 Coordinating Investigator: An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

1.20 Contract Research Organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see section 8. "Essential Documents for the Conduct of a Clinical Trial").

1.24 Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations, and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance.

1.28 Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

1.29 Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical): Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB): An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator/Institution: An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements."

1.36 Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects (see section 7. "Investigator's Brochure").

1.37 Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

1.39 Monitoring Report: A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

1.41 Nonclinical Study: Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee): The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record: See Source Documents.

1.44 Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance, the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

1.47 Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guidance, the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections (see section 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

(See the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

1.51 Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

1.53 Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

1.59 Trial Site: The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

1.61 Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

- Approval/favorable opinion;
- Modifications required prior to its approval/favorable opinion;
- Disapproval/negative opinion; and
- Termination/suspension of any prior approval/favorable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

3.1.6 When a nontherapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see sections 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s)

adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see section 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions, and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.
(b) At least one member whose primary area of interest is in a nonscientific area.
(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see sections 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded,

the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see section 1.21) to all trial- related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial/study reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see section 6.), the ICH Guidance for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol, and conduct.

5.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

(b) Maintain SOPs for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see sections 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see section 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the appropriate regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed (see section 4.9.5).

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see sections 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;

(b) To comply with procedures for data recording/reporting: and

(c) To permit monitoring, auditing, and inspection (see section 4.1.4).

(d) To retain the essential documents that should be in the investigator/institution files (see section 8.) until the sponsor informs the investigator/institution these documents are no longer needed (see sections 4.9.4, 4.9.5, and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Duties and Functions

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)), should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available. (See section 7. "Investigator's Brochure.")

5.13 Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 **Purpose** The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

5.18.2 **Selection and Qualifications of Monitors**

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 **Extent and Nature of Monitoring**

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 **Monitor's Responsibilities**

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see sections 4.1, 4.2, 5.6) and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorized procedures.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents. (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 **Monitoring Procedures**

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 **Monitoring Report**

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 **Purpose**

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 **Selection and Qualification of Auditors**

(a) The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor’s qualifications should be documented.

5.19.3 **Auditing Procedures**

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings.

(e) Where required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial/study reports in marketing applications meet the standards of the ICH Guidance for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guidance for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicenter Trials

For multicenter trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of the coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including (for example):

(a) Randomization.
(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for

subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Recordkeeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with

the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guidance delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator- sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guidance.

7.2 General Considerations

The IB should include:

7.2.1 **Title Page** This should provide the sponsor's name, the identity of each

investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 **Confidentiality Statement** The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 **Table of Contents** An example of the Table of Contents is given in Appendix 2.

7.3.2 **Summary** A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 **Introduction** A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 **Physical, Chemical, and Pharmaceutical Properties and Formulation**

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 **Nonclinical Studies**

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

Species tested;
Number and sex of animals in each group;
Unit dose (e.g., milligram/kilogram (mg/kg));
Dose interval;
Route of administration;
Duration of dosing;
Information on systemic distribution;
Duration of post-exposure follow-up;
Results, including the following aspects:

- Nature and frequency of pharmacological or toxic effects;
- Severity or intensity of pharmacological or toxic effects;
- Time to onset of effects;
- Reversibility of effects;
- Duration of effects;
- Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

Single dose;
Repeated dose;
Carcinogenicity;
Special studies (e.g., irritancy and sensitization);
Reproductive toxicity;
Genotoxicity (mutagenicity).

7.3.6 **Effects in Humans**

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function).

Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s)).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 **Summary of Data and Guidance for the Investigator**

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 Appendix 1

TITLE PAGE OF INVESTIGATOR'S BROCHURE (Example)

Sponsor's Name:

Product:

Research Number:

Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 Appendix 2

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

- Confidentiality Statement (optional)

- Signature Page (optional)

1. Table of Contents

2. Summary

3. Introduction

4. Physical, Chemical, and Pharmaceutical Properties and Formulation

5. Nonclinical Studies
    - 5.1 Nonclinical Pharmacology
    - 5.2 Pharmacokinetics and Product Metabolism in Animals
    - 5.3 Toxicology

6. Effects in Humans
    - 6.1 Pharmacokinetics and Product Metabolism in Humans
    - 6.2 Safety and Efficacy
    - 6.3 Marketing Experience

7. Summary of Data and Guidance for the Investigator

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter.

Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	Information given to trial subject - Informed consent form (Including all applicable translations)	To document the informed consent	X	X
	- Any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.6	Signed agreement between involved parties, e.g.: - Investigator/institution and sponsor - Investigator/institution and CRO - Sponsor and CRO - Investigator/institution and authority(ies) (Where required)	To document agreements	 X X X	 X X (where required) X X
8.2.7	Dated, documented approval/favorable opinion of IRB/IEC of the following: - Protocol and any amendments - CRF (if applicable) - Informed consent form(s) - Any other written information to be provided to the subject(s) - Advertisement for subject recruitment (if used) - Subject compensation (if any) - Any other documents given approval/favorable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	X	X
8.2.8	Institutional review board/independent ethics committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	Regulatory authority(ies) authorization/approval/ notification of protocol (where required)	To document appropriate authorization/approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
8.2.12	Medical/laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
8.2.15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
8.2.16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial.		X
8.2.17	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applic-able)
8.2.18	Master randomization list	To document method for randomization of trial population		X (third party if applicable)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.19	Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	Any revisions to: - Protocol/amendment(s) and CRF - Informed consent form - Any other written information provided to subjects - Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents that take effect during trial	X	X
8.3.3	Dated, documented approval/favorable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the following: - Protocol amendment(s) - Revision(s) of: - Informed consent form - Any other written information to be provided to the subject - Advertisement for subject recruitment (if used) -Any other documents given approval/favorable opinion - Continuing review of trial (see section 3.1.4)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X
8.3.4	Regulatory authority(ies) authorizations/ approvals/notifications where required for: - Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	Curriculum vitae for new investigator(s) and/or subinvestigators	(See section 8.2.10)	X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.6	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see section 8.2.11)	X	X
8.3.7	Updates of medical/ laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document that tests remain adequate throughout the trial period (see section 8.2.12)	X (where required)	X
8.3.8	Documentation of investigational product(s) and trial-related materials shipment	(See section 8.2.15)	X	X
8.3.9	Certificate(s) of analysis for new batches of investigational products	(See section 8.2.16)		X
8.3.10	Monitoring visit reports	To document site visits by, and findings of, the monitor		X
8.3.11	Relevant communications other than site visits - Letters - Meeting notes - Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see section 8.2.3)	X	
8.3.13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	Signed, dated, and completed case report forms (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	Documentation of CRF corrections	To document all changes/ additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 4.11.2 and 5.16.2	X (where required)	X
8.3.18	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
8.3.21	Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	X	
8.3.22	Subject enrollment log	To document chronological enrollment of subjects by trial number	X	
8.3.23	Investigational product(s) accountability at the site	To document that investigational products(s) have been used according to the protocol	X	X
8.3.24	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
8.3.25	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
8.4.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	Audit certificate (if required)	To document that audit was performed (if required) (see section 5.19.3(e))		X
8.4.5	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	Final report by investigator/institution to IRB/IEC where required, and where applicable, to the regulatory authority(ies) (see section 4.13)	To document completion of the trial	X	
8.4.8	Clinical study report (see section 5.22)	To document results and interpretation of trial	X (if applicable)	X