CHAPTER 48 – Bioresearch Monitoring

SUBJECT: SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS	IMPLEMENTATION DATE April 19, 2017
REVISION:	COMPLETION DATE Continuing

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
FACTS does not require product codes for Bioresearch Monitoring Inspections	09810 Food Additives
	41810 Biologics (Human Cellular, Tissue, and Gene Therapies)
	42810 Biologics (Blood and Blood Products)
	45810 Biologics (Vaccines and Allergenic Products)
	48810 Human Drugs
	68810 Animal Drugs
	83810 Medical Devices
	98810 Tobacco Products

FIELD REPORTING REQUIREMENTS:

For domestic inspections, copies of all establishment inspection reports (EIRs), complete with attachments, exhibits, and any post-inspectional correspondence are to be submitted promptly to the Center contact, who is generally the reviewer in the Center's Bioresearch Monitoring (BIMO) program identified in the assignment.

For foreign inspections, all original EIRs, complete with attachments, unlabeled exhibits and any related correspondence are to be submitted promptly to the Center contact identified in the assignment.

For both domestic and foreign inspections, a preliminary summary of findings should be submitted via email to the Center contact as soon as possible after the inspection has completed.

All EIRs should be completed in accordance with Field Management Directive (FMD) No. 86, Establishment Inspection Report (EIR) – Inspection Conclusions and District Decisions (http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm061430.htm). When a Form FDA 483, "Inspectional Observations" (483), is issued, a copy should be forwarded to the Center contact (by facsimile, e-mail, or placement in the appropriate shared folder, as agreed to with the Center), generally no later than 3 business days.

PART I - BACKGROUND

Since the Investigational New Drug (IND) Regulations went into effect in 1963, the Food and Drug Administration (FDA) has exercised oversight of the conduct of clinical studies involving FDA-regulated products. The BIMO Program was established in 1977 by a task force that included representatives from the drug, biologic, device, animal drug, and food areas.

Compliance programs (CP) were developed to provide uniform guidance and specific instructions for inspections of Clinical Investigators (CP 7348.811), Sponsors (CP 7348.810), In-Vivo Bioequivalence facilities (CP 7348.001), Institutional Review Boards (CP 7348.809), and Nonclinical Laboratories (CP 7348.808).

Regulations addressing requirements of clinical investigators, sponsors and monitors of human drugs and biologics studies (21 CFR Parts 312 and 314) were published on March 19, 1987, and became effective on June 17, 1987. The animal drug regulations (21 CFR Parts 511 and 514) were published on May 27, 1975. Regulations for clinical investigations of devices (21 CFR Part 812) were published on January 18, 1980, and for premarket approval of medical devices (21 CFR Part 814) on July 22, 1986.

These regulations establish specific responsibilities of sponsors for ensuring (1) the proper conduct of clinical studies for submission to FDA and (2) the protection of the rights and welfare of subjects involved in clinical studies. The specific responsibilities of sponsors of clinical studies include obligations to:

1) Obtain agency approval, where necessary, before studies begin.

2) Manufacture and label investigational products appropriately.

3) Initiate, withhold, or discontinue clinical trials as required.

4) Refrain from commercialization of investigational products.

5) Control the distribution and return of investigational products.

6) Select qualified investigators to conduct studies.

7) Disseminate appropriate information to investigators.

8) Select qualified persons to monitor the conduct of studies.

9) Adequately monitor clinical investigations.

10) Evaluate and report adverse experiences.

11) Maintain adequate records of studies.

12) Submit progress reports and the final results of studies.

Sponsors may transfer responsibility for any or all of these obligations to Contract Research Organizations (CROs). [Note: The medical device regulations (21 CFR Part 812) do not define or delineate responsibilities for CROs. Device study sponsors are therefore held responsible for any regulatory noncompliance by a CRO.] Under the regulations such transfers of responsibility are permitted by written agreement. Responsibilities that are not specified in a written agreement are not considered to be transferred. When operating under written agreements, the CROs are subject to the same regulatory actions as sponsors for any failure to perform any of the obligations assumed.

Monitors are employed by sponsors or CROs to oversee the progress of an investigation.

A sponsor-investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational article is administered, dispensed or implanted. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor. See CP 7348.811 for Clinical Investigators and Sponsor-Investigators.[1]

[1] See http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf.

PART II - IMPLEMENTATION

A. OBJECTIVES

The objectives of the BIMO Program are:

1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;

2. To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and

3. To assess compliance with FDA's regulations governing the conduct of clinical trials.

The purpose of this compliance program is to provide instructions to the field and Center personnel for conducting inspections of sponsors, contract research organizations (CROs), and monitors, and recommending associated administrative/enforcement actions.

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. Coverage

   This program covers domestic and foreign inspections of:

   a. Sponsors

      Such entities consist of those individuals, organizations, or corporations that initiate clinical investigations and have been so identified by FDA through receipt of an investigational exemption, or application for research or marketing permit for an article. A sponsor is defined in the regulations at 21 CFR 312.3(b), 510.3(k), and 812.3(n).

   b. Contract Research Organizations

      Such entities consist of those organizations or corporations that have entered into a contractual agreement with a sponsor to perform one or more of the obligations of a sponsor (e.g., design of protocol, selection of investigators and study monitors, evaluation of reports, and preparation of materials to be submitted to FDA). In accord with 21 CFR 312.52 and 511.1(f), responsibility as well as authority may be transferred and thus the CRO becomes a regulated entity. [Note: As noted above, the medical device regulations (21 CFR Part 812) do not provide for the transfer of sponsor regulatory obligations to CROs. Device study sponsors are therefore held responsible for any regulatory noncompliance by a CRO.]

c. Monitors

Such entities consist of those individuals who are selected by either a sponsor or CRO to oversee the clinical investigation. The monitor may be an employee of the sponsor or CRO, or an independent consultant to the sponsor or the CRO. The latter are commonly referred to as clinical research associates (CRAs).

2. Inspection Assignments

a. Center BIMO units issue inspection assignments of sponsors, CROs, and monitors.

i. Domestic inspection assignments are issued to the district offices.

ii. International inspections of sponsors are generally assigned when the sponsor is located outside of the United States (US) and an overall view of the conduct of the study, as provided at the sponsor site, is critical to decision-making on product approval. International inspection assignments are issued to the ORA Headquarters (HQ) BIMO contact.

b. The assignment should identify:

i. The program assignment code (PAC) and Field Accomplishments and Compliance Tracking System (FACTS) number;

ii. The name, address and phone number (and e-mail address, if available) of the sponsor/CRO/monitor to be inspected; for international inspections, the U.S. agent's contact information.

iii. The type and purpose of the inspection;

iv. The background materials (e.g., study protocol and amendments, relevant sections of marketing applications/submissions, case report forms (CRFs), the sponsor's/CRO's/monitor's compliance history) sent from the Center to facilitate the inspection. For investigational device studies, the Center should identify the type of study (i.e., significant risk (IDE), non-significant risk (abbreviated requirements), or IDE exempt).

v. Specific issues or concerns (if applicable) that need to be addressed during the inspection; if the assignment requests review of information and/or data for one or more of the study sites, line data and protocol deviations submitted by the sponsor for the site(s) in question may be included in the background materials.

vi. The due date for the Center contact to receive the completed EIR;

vii. The headquarters address where the EIR should be sent; and

viii. The name, telephone number, e-mail address, and fax number of the Center BIMO contact(s).

c. When requesting expedited inspections, the Center should provide justification. If a Center's assignment needs high priority, follow Field Management Directive (FMD) No. 17, ORA (Office of Regulatory Affairs) Field Assignments - Guidelines for Issuance by Headquarters (http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm056651.htm)

d. If the sponsor has contracted out all or part of their responsibilities, the field investigator should notify the Center contact of this fact and continue the inspection. The Center will decide whether to follow up with an inspection at the CRO or monitor and issue any additional assignments.

e. Whether a study monitor is an employee of the sponsor or CRO or is an independent CRA, a monitor inspection will cover the monitor's obligations for overseeing the investigation as instructed in Part III.

f. All headquarters and field personnel who become aware of complaints or problems related to a sponsor/CRO/monitor are encouraged to refer the name(s) to the appropriate Center with a recommendation for inspection. All recommendations should include the following:

i. The name, address, and phone number (and e-mail address, if available) of the sponsor/CRO/monitor;

ii. If available, the name(s) of the test article(s) being investigated, and the application for research or marketing permit number(s); and

iii. The basis for the recommendation and any relevant documentation.

3. Communication between the Centers and the Districts

Inspectional observations documenting that a sponsor/CRO/monitor is not operating in compliance with regulations governing the conduct of clinical trials may be used as evidence for taking appropriate administrative and/or enforcement actions. Ensuring that the evidence collected to support such actions is both appropriate and adequate requires that communication lines between the field investigator and the Center be established early and maintained throughout the entire process, i.e., until post-inspectional correspondence is issued by the Center.

a. Prior to an Inspection

i. The Center issues an assignment (B. 2. above) that includes contact information for the BIMO reviewer.

ii. The field investigator contacts the BIMO reviewer:
- Upon receipt of the assignment, to establish initial contact and/or provide an inspection start date;
- When the inspection date is firmly set, to alert the BIMO reviewer and/or a back-up to be available and to establish the most appropriate means of contact for both the investigator and the BIMO reviewer/back-up;
- To obtain any information that may change the focus of the inspection;
- To coordinate inspection arrangements if Center personnel plan to participate in the inspection

iii. Special Considerations.

In particular cases, the Center may arrange for a consultative teleconference immediately prior to the inspection(s) if, for example, the complexity of the product or study, data concerns, urgency of feedback, compliance history, etc., trigger the need to discuss issues further. Such conference calls are most likely when the agency is reviewing Biologics License Applications (BLAs), New Drug Applications (NDAs), Premarket Approval Applications (PMAs), or New Animal Drug Applications (NADAs) for novel or complex products, or in "for cause" inspections where pertinent information is either complex or needs discussion between the Center and the field. The assignment will usually state that this teleconference will occur, unless information necessitating this discussion emerges after the assignment is issued.

These teleconferences may include the following participants, as warranted and feasible:
- BIMO reviewer (and supervisor/division director or other staff, as appropriate);
- Lead application reviewer (along with branch and division chiefs, as appropriate) and other application reviewers as needed; and
- Field investigator(s) assigned to the inspection(s) and/or the BIMO coordinator (when not yet specifically assigned). Other district staff may also participate.

b. During an Inspection

i. The BIMO reviewer contacts the field investigator if significant new information becomes available.

ii. The field investigator contacts the BIMO reviewer or designated back-up person if he/she:
- Needs advice or clarification. The BIMO reviewer and field investigator should strive to be accessible to one another as much as possible during the time that the inspection is going on.

- Uncovers other evidence of concern warranting discussion with Center staff.

c. After an Inspection

i. Within three (3) business days of concluding the inspection, the field investigator forwards to the BIMO reviewer (by facsimile, e-mail, or placement in the appropriate shared drive folder, as agreed to with the Center) any 483 that is issued.

ii. The field investigator forwards as soon as possible to the BIMO reviewer a copy of any response to the 483 by the inspected party. The BIMO reviewer forwards to the field investigator, a copy of any response to a 483 that does not appear to have been shared with the inspecting district.

iii. The BIMO reviewer consults with the field investigator as needed when reviewing the EIR.

iv. The Center consults with appropriate District personnel if contemplating an EIR classification different from the one recommended by the District.

v. If the Center's final classification is different from the one recommended by the field, the Center should ensure that District personnel are aware of the change and reasons for the change. The Center promptly forwards, to the field investigator and other appropriate district personnel, by e-mail if possible, copies of post-inspectional correspondence issued to the inspected party.

vi. The Center enters the final classification into FACTS.

4. Responsibilities of Field Investigators, Inspection Team Leaders, and Headquarters Participants

a. The field investigator's responsibilities include, but are not limited to, the following:

i. Attending pre-inspection conferences if and when scheduled;

ii. Scheduling and conducting the assigned inspection;

iii. Discussing with District management the need to adjust the workload in order to meet specific deadlines (e.g., deadline imposed for review of the application by the Prescription Drug/Animal Drug/Medical Device User Fee Act);

iv. Communicating inspectional issues and observations with the sponsor, CRO, or monitor during the course of the inspection, as appropriate;

v. Communicating inspectional observations and issues with the Center contact, as directed in the assignment memorandum;

vi. Preparing, issuing, and discussing the items listed on the 483 with the inspected party; and

vii. Participating in discussions with the Center regarding potential changes in the EIR classification.

b. Inspection Team Leader

When inspections are conducted by a team, a field investigator serves as inspection team leader and is responsible for the cooperative conduct of the inspection. The team leader's responsibilities include, but are not limited to, the following (see also Investigations Operations Manual (IOM), Team Inspections, https://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf):

i. Attending pre-inspection conferences if and when scheduled;

ii. Scheduling and coordinating the participation of team members;

iii. Discussing inspection plans and objectives with team members;

iv. Setting team policy regarding communications with the sponsor, CRO, or monitor;

v. Assuring that team members understand their roles in conducting the inspection, taking notes, collecting documentation, preparing sections of the inspection report and exhibits, and signing the report;

vi. Discussing personal conduct with team members as necessary; and

vii. Resolving disputes or differences of opinion among team members, including items to be listed on the 483.

c. Headquarters Participants

A headquarters participant is a member of the inspection team who serves in a compliance or scientific advisory capacity to the Team Leader. The headquarters participant's responsibilities include, but are not limited to, the following:

i. Identifying specific objectives to be covered by the inspection;

ii. Providing information pertinent to the inspection;

iii. Completing the Inspection Participation Form (Form FDA 2115, available at http://inside.fda.gov:9003/downloads/Administrative/Forms/FDA/UCM030799.pdf) and submitting it to the Office of Security Operations (OSO, Special Programs Branch (White Oak, Building 1, Room 1201, 10903 New Hampshire Avenue, Silver Spring, MD 20993). The form may also be submitted electronically to FDA-ORA Credentials (located in Microsoft Global Address list). For further information see http://inside.fda.gov:9003/EmployeeResources/FDABadging/GeneralInformation/default.htm;

iv. Obtaining inspection credentials as directed by OSO;

v. Attending pre-inspection conferences if and when scheduled;

vi. Participating in the on-site inspection as permitted by agency priorities; and

vii. Providing guidance and expertise during the inspection, and preparing specific sections of the inspection report within timeframes established by the Team Leader.

5. Resolution of Disagreements

If there is disagreement among members of the inspection team, the issue should be discussed off-site and resolved cooperatively. Any difficulties in conducting team inspections should be discussed with both District management and the assigning Center, and, if not resolved, immediately referred to the ORA HQ BIMO contact.

6. Inspections of the Veteran's Administration (VA) as the sponsor of FDA-regulated clinical trials. (For example, the VA's Cooperative Studies Program sponsors a number of FDA-regulated clinical trials.)

a. Pre-Inspection

Center. The BIMO unit in the assigning Center will provide the VA's Office of Research Oversight (ORO) with written notification of FDA's intention to inspect a VA sponsor program at the time an assignment is being issued to the field. Information on the VA's ORO is at: http://www.va.gov/ORO/about_us.asp#sthash.ABGMdXOR.dpuf.

This notice should be sent to:

Executive Director
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs

810 Vermont Avenue, N.W., Suite 574
Washington, D.C. 20420

Field. The field investigator will contact the Medical Center Director/VA sponsor program before the inspection, as they would any other sponsor they are assigned to inspect.

b. Post-Inspection

The Center will provide the VA's ORO redacted copies of post-inspection correspondence issued to VA sponsored programs that include a discussion of deficiencies noted during the inspection (including the FDA-483s). Such materials should be sent to:

Executive Director
Office of Research Oversight (10R)
Veterans Health Administration
Department of Veterans Affairs
810 Vermont Avenue, N.W., Suite 574
Washington, D.C. 20420

If, following receipt of the FDA correspondence, the VA-ORO requests a copy of the EIR, a redacted copy of the report will be provided to VA-ORO by the district office.

PART III - INSPECTIONAL

Inspections involve evaluation of the sponsor's/CRO's/monitor's practices and procedures to determine compliance with applicable regulations.

A. GENERAL

The following pertain to all inspections.

1. Sponsor, CRO, and monitor inspections are product type-specific, i.e., human drugs and biologics, animal drugs, medical devices, or foods. Field investigators must apply the pertinent regulations to each inspection.

2. Inspections under this program will be pre-announced unless otherwise instructed in the inspection assignment. The field investigator should keep the time span between initial contact and actual inspection as short as possible. The field investigator should immediately report to the Center contact any attempt by the sponsor/CRO/monitor to unduly delay an inspection, by more than ten working days, without sufficient justification.

3. Inspection Refusals

   a. Refusal of entry

   If a sponsor/CRO/monitor refuses to permit an inspection by FDA personnel, the field investigator should inform the sponsor/CRO/monitor of the agency's legal authority[2] to conduct such inspections. If entry is still refused, the investigator should issue the completed Form FDA 482 (Notice of Inspection) to the most responsible person available and leave the premises. The investigator should immediately notify his/her supervisor, the assigning Center contact, and ORA HQ BIMO contact of this refusal.

   b. Refusal of Information

   If at any time during the inspection, the sponsor/CRO/monitor refuses to allow FDA personnel access to or copying of records to which FDA is entitled under the law and regulations, the field investigator should inform the sponsor/CRO/monitor about the agency's legal authority[3] to access the information. If access to or copying is still refused, the field investigator should continue with the inspection and notify his/her supervisor, the assigning Center contact and ORA HQ BIMO contact. The same procedure should be followed when it becomes evident that delays by the sponsor/ CRO/monitor are such that they constitute a de facto (i.e., actual) refusal.

   When a refusal of entry or refusal to supply necessary information cannot be resolved by the assigning Center contact or ORA HQ BIMO contact and it is deemed necessary to pursue an inspection warrant, follow the procedures in the Regulatory Procedures Manual, Section 6-3, Inspection Warrants,

[2] See Sections 301(f) and 704 of the Federal Food, Drug and Cosmetic Act (FFDCA), Sections 351(c), 360A(a), (b) & (f); 360B(a); and 361(a) of the Public Health Service (PHS) Act, and 21 CFR 312.68 and 812.145.
[3] See Sections 301(f) and 704 of the FFDCA, section 351(c) of the PHS Act, and applicable regulations (e.g., 21 CFR 312.68, 812.145(c)).

and notify the Office of Enforcement and Import Operations (OEIO)/Division of Enforcement (DE).

4. Each inspection will consist of an evaluation of the practices and procedures of sponsors, CROs, and monitors in the particular study(s), using the investigational plan in the research or marketing application/submission, applicable regulations, and any specific directives in the inspection assignment.

5. Field investigators who observe or suspect deviations from the regulations that affect data integrity or endanger subject rights, safety, or welfare should immediately discuss their observations with their supervisor, and the assigning Center contact and continue the inspection. The assigning Center will promptly determine if the inspection should be expanded or modified and provide direction on how to proceed in order to obtain appropriate documentation for the noted observations.

6. The field investigator issues a 483 at the conclusion of the inspection when deviations from regulations are observed. Inspectional observations listed on the 483 **must** be based on the regulations. **Approaches that differ from those described in FDA's guidance documents should not be listed on the 483 unless they constitute deviations from the regulations.** Observed deviations from guidance may be discussed with the sponsor/CRO/monitor during the exit interview, however, and reported in the EIR. The field investigator encourages the sponsor/ CRO/monitor to submit a prompt written response to the District Office and Center regarding any inspection observations listed on the 483.

B. INSPECTION PROCEDURES

The Center may provide background information and special instructions with the inspection assignment. The following outline provides only the minimum scope of the inspection, and each field investigator should expand the inspection as the circumstances warrant. Inspections should be sufficient in scope to cover special instructions in the assignment and to determine if the sponsor's/CRO's/monitor's practices and procedures comply with the appropriate regulations. The field investigator should **not** attempt to scientifically evaluate the study data or protocol(s).

Any deviations from regulations should be thoroughly **documented**. For example, if the sponsor failed to review monitoring reports in a timely fashion and/or failed to bring non-compliant clinical investigators into compliance, monitoring reports, report review dates, and evidence of clinical investigator continued non-compliance should be **documented** and **copied**. Discuss potential violations involving fraud subject to Title 18 of the United States Code (18 U.S.C.) with your supervisor, and assigning Center contact for appropriate referral to the Office of Criminal Investigations (OCI).

C. ORGANIZATION AND PERSONNEL

1. **Determine** the overall organization of the clinical research activities and monitoring of the selected studies.

2. **Obtain** relevant organizational charts that document structure and responsibilities for all activities involving investigational products.

    a. **Identify** all departments, functions, and key individuals responsible for areas of sponsor activities such as protocol development, selection of investigators, statistical analysis, clinical supplies, monitoring, and quality assurance.

    b. **Determine** who has the authority to review and approve study reports and data listings.

    c. **Determine** who is responsible for final evaluations and decisions in the review of adverse events and safety information.

3. **Obtain** a list of outside services and contractors (CROs, monitors, laboratories, IRBs) and **document** the services they provide and who is responsible for their selection and oversight. Also **document** the accurate location/address of these contracted parties.

    a. When a sponsor transfers responsibility for their obligations to a CRO:

        i. **Obtain** a copy of any written agreement transferring responsibilities. If there is a separate transfer of regulatory obligations (TORO) document, obtain a copy of it as well.

        ii. **Determine** if the transfer of responsibilities was submitted to the agency as required by 21 CFR 312.23(a)(1)(viii), 314.50(d)(5)(x), 511.1(b)(4)(vi), and 514.1(a)(8)(viii). [As noted above, device regulations (21 CFR Part 812) do not provide for the transfer of regulatory obligations to CROs. Device study sponsors are therefore held responsible for any regulatory noncompliance by a CRO.]

        iii. **Document** any instance where transfer of responsibilities was not reported to the agency.

    b. If a CRO is contracted to perform an obligation of the sponsor for managing adverse event/safety information (e.g., including activities such as collecting, evaluating, or reporting such information), **obtain** information that identifies the responsibilities of each party.

4. **Obtain** a list of all monitors (for the studies being inspected) along with their job descriptions and qualifications.

D. REGISTRATION OF STUDIES ON CLINICALTRIALS.GOV

As a result of Public Law 105-115, known as the Food and Drug Administration Modernization Act of 1997, the National Library of Medicine (NLM) within the National Institutes of Health (NIH) developed an Internet-based registry and results data bank for clinical trials of drugs, including biological products, for serious or life-threatening conditions. On September 27, 2007, Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) broadened the scope of the ClinicalTrials.gov (CT.gov) registry to "applicable clinical trials" (ACTs) for all diseases and conditions and outlined requirements for submitting registration, summary results, and adverse events information for ACTs of drug products (including biological products) and device products, as well as pediatric post market surveillances of device products, to the clinical trial databank. On November 21, 2014, a Notice of Proposed Rulemaking was published in the Federal Register (79 FR 69566) to implement and expand the CT.gov submission requirements in Title VIII of FDAAA. On September 21, 2016, the Final Rule was published in the Federal Register (81 FR 64982) and is codified at 42 CFR Part 11 (CT.gov regulations). The Final Rule became effective on January 18, 2017, and a responsible party (RP) had until April 18, 2017, to come into compliance with the Final Rule's requirements.

FDAAA also requires that a certification of compliance accompany certain human drug, biological, and device product submissions made to FDA.[4] (The certification requirement went into effect on December 26, 2007.) FDA has developed Form FDA 3674 to assist sponsors, applicants, and submitters of INDs, NDAs, BLAs, PMAs, HDEs, and 510(k)s with this certification. With submission of this form, sponsors and others certify to FDA that they have complied with the applicable requirements to submit clinical trial information for inclusion in the CT.gov databank. As stated in the guidance regarding this certification, Form FDA 3674 is recommended to accompany the following types of applications and submissions[5]:

- IND
- New Clinical Protocol submitted to an IND
- NDA
- Efficacy Supplement to an approved NDA
- BLA
- Efficacy Supplement to an approved BLA
- ANDA
- PMA
- PMA Panel Track Supplement
- HDE.
- 510(k) that refers to, relates to, or includes information on a clinical trial

[4] Section 801 of FDAA amended the PHS Act by adding this certification requirement under section 402(j)(5)(B) (codified at 42 U.S.C. 282(j)(5)(B)).

[5] See section 402(j)(5)(B) of the PHS Act for statutory requirement. The guidance document on completion of the certification form is available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm.

Specifics regarding CT.gov registration and results information submission requirements are available at https://clinicaltrials.gov/ct2/manage-recs/fdaaa. The CT.gov regulations require that a "responsible party" (in general, the sponsor or designated principal investigator) register and report results information for an applicable clinical trial.[6]

Applicable clinical trials, as defined in 42 CFR Part 11, are:

1. For drugs, including biological products:
   Controlled clinical investigations, *other than Phase I clinical investigations*, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (42 U.S.C. 262), where "clinical investigation" has the meaning given in 21 CFR 312.3 and "phase 1" has the meaning given in 21 CFR 312.21.

   A clinical trial of a combination product with a drug primary mode of action under 21 CFR Part 3 is also an ACT, provided that it meets all other criteria of the definition under this part.[7]

2. For device products:
   A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);

   A pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360l); or

   A clinical trial of a combination product with a device primary mode of action under 21 CFR Part 3, is also an ACT, provided that it meets all other criteria of the definition under this part.[8]

In general, applicable clinical trials must be registered within 21 calendar days of enrollment of the first subject.[9] A pediatric postmarket surveillance of a device product that is not a clinical trial must be registered no later than 21 days after FDA approves the postmarket surveillance plan.[10]

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[6] See 42 CFR 11.10(a) - Responsible Party (RP) means 1) the sponsor of the clinical trial as defined by 21 CFR 50.3; 2) if so designated by a sponsor, grantee, contractor, or awardee, the principal investigator (PI) of the clinical trial who is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results information about the trial, and has the ability to meet all of FDAAA's requirements for submission of clinical trial information; or 3) the entity whom FDA orders to conduct pediatric postmarket surveillance of a device product.

[7] See 42 CFR 11.10(a). See also ClinicalTrials.gov Protocol Data Element Definitions for Interventional and Observational Studies (February 7, 2017) for a complete list of the required elements for registration.

[8] See footnote 7.

[9] See 42 CFR 11.24(a). See also 42 CFR 11.10(a) –" Enroll or enrolled means a human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR Part 50 and/or 45 CFR Part 46, as applicable. For purposes of this part, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol."

[10] See 42 CFR 11.24(b)(2).

Consistent with the applicable statutory and regulatory provisions above:

1. **Determine** whether the study or studies being inspected for a submission or application submitted to FDA is an applicable clinical trial. Consult with the Center as needed.

2. **Determine** the responsible party (RP) for the applicable clinical trial. If the sponsor is not the RP, determine what party has been delegated the RP role and the address and contact information for the RP.

3. If the study/studies is/are applicable clinical trial(s), **determine** whether the study or studies were registered on CT.gov.

4. **Identify** the National Clinical Trial number (i.e., NCT number) for the study or studies listed on CT.gov.

5. **Compare** the date of registration to the **actual date of** the first subject's enrollment in the study. Determine whether the study or studies were registered not later than 21 days of enrollment of the first subject.[11]

   For a pediatric postmarket surveillance of a device product that is not a clinical trial determine whether the study was registered within 21 days after FDA approved the postmarket surveillance plan.

6. **Determine** the study's or studies' completion date (aka "Primary Completion Date"[12]), which is the date the final subject was examined or received an intervention for purposes of final collection of data for the primary outcome.

   If greater than one year since the Primary Completion Date, has summary results information for primary outcomes been submitted to CT.gov, including a copy of the study protocol?[13]

   For a pediatric postmarket surveillance of a device product that is not a clinical trial, the completion date is the date on which the final report of the pediatric postmarket surveillance of the device product is submitted to FDA. For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party must submit clinical trial results information not later than 30 calendar days after the date on which the final report was submitted to FDA.

7. **Determine** the study's or studies' "Study Completion Date," defined as the date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (e.g., last subject's last visit). Determine whether the clinical trial concluded according to the pre-specified protocol or was terminated[14].

[11] See 42 CFR 11.10(a) & 11.10(b)(17).
[12] See footnote 11.
[13] See 42 CFR 11.44.
[14] See 42 CFR 11.10(a)

If greater than one year since the Study Completion Date, have results information for secondary outcomes and adverse events been submitted to CT.gov?

8. **Determine** whether the responsible party has completed and submitted the Form FDA 3674.

9. When examining informed consent documents related to an ACT registered on CT.gov, **determine** whether the appropriate required statement referencing CT.gov is included. 21 CFR 50.25(c). The statement is:

   ''A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.''

E. SELECTION AND MONITORING OF CLINICAL INVESTIGATORS

1. **Obtain** a list of all investigators and **determine** if there is a Form FDA 1572 (21 CFR 312.53(c)(l) or a signed investigator agreement (21 CFR 812.43(c)) for each clinical investigator identified.

2. Regulations require that the sponsor/CRO select clinical investigators qualified by training and experience (21 CFR 312.53(a), 511.1(b)(7)(i), and 812.43(a)). **Determine** the sponsor's/CRO's criteria for selecting clinical investigators.

3. **Determine** if the sponsor/CRO provided the investigators with all necessary information prior to initiation of the clinical trial. This may include clinical protocols or investigational plans, labeling, investigator brochures, and previous study experience.

4. **Determine** how the sponsor/CRO handles serious deviations from the approved investigational plan (which includes the study protocol) or FDA regulations.

5. **Determine** if the sponsor/CRO/monitor identified any clinical investigators who did not comply with the investigational plan or FDA regulations. If so, did the sponsor/CRO secure prompt compliance? (When there is a CRO, **determine** who has the responsibility to follow up on noncompliance and secure investigator compliance, the sponsor or the CRO.) When instances of continued clinical investigator noncompliance are identified, **obtain** evidence of prompt correction or termination of the investigator's participation in the study.

6. **Identify** any clinical investigator sites where studies were terminated and the circumstances involved. **Review** monitoring reports for those clinical investigators and **determine** if those instances were promptly reported to FDA as required by 21 CFR 312.56(b). [Since termination of an investigator's participation in a device study would require return or disposal of the investigational device(s), a report is likewise required under 812.150(b)(6).]

7. **Identify** any non-compliant clinical investigators who were neither brought into compliance nor removed from the study (participation in the study terminated) by the sponsor as required by 21 CFR 312.56(b) and 812.46(a). **Determine** the reason their participation in the study was not terminated.

F. SELECTION OF MONITORS

1. **Review** the criteria for selecting monitors and determine if monitors meet those criteria.

2. **Determine** how the sponsor/CRO allocates responsibilities when more than one individual is responsible for monitoring functions, e.g., a medical monitor may have the responsibility for medical aspects of the study (and may be a physician) while other monitors may assess regulatory compliance.

G. MONITORING PROCEDURES AND ACTIVITIES

With the prevalence of multisite clinical trials, traditional monitoring techniques – early and frequent on-site visits at all clinical sites – have become resource intensive. Regulations do not prescribe a specific monitoring technique, simply stating that sponsors are required to select monitors qualified by training and experience to monitor the investigational study (21 CFR 312.53(d), 511.1(b)(8)(ii), and 812.43(d)). Reference the sponsor's/CRO's/monitor's procedures (written SOPs or procedures or stated practices) for the following.

1. Procedures

    a. **Review** the procedures, frequency, scope, and process the sponsor/CRO/monitor uses to monitor the progress of the clinical investigation. (Device regulations (21 CFR 812.25(e)) require written monitoring procedures as part of the investigational plan.)

    b. **Obtain** a copy of the sponsor's/CRO's/monitor's written procedures (SOPs and guidelines) for monitoring and **determine** if the procedures were followed for the selected study. In the absence of written procedures, conduct interviews of the monitors as feasible and/or otherwise **determine** how monitoring was conducted.

2. Activities

    a. **Review** pre-trial and periodic site-visit (monitoring) reports. When reviewing monitoring reports, **determine** when they were reviewed by the sponsor/CRO and, where clinical investigator noncompliance with the investigational plan or regulations was indicated, what follow-up was initiated and how quickly action was taken by the sponsor/CRO.

    b. **Determine** if the sponsor/CRO/monitor assured, through documentation, that the clinical investigation was conducted in accordance with the investigational plan submitted to FDA.

c. **Determine** if there is documentation that the responsibilities of the clinical investigators were carried out according to the FDA regulatory requirements (21 CFR 312.60. 312.61, 312.62, 312.64, 312.66, 312.68, (312.69 if the investigational

product is a controlled substance), 812.100, 812.110, 812.140(a), (d), and (e), and 812.150(a)).

3. Review of Site Records

a. **Determine** if monitoring visits included a comparison of individual subject records and other source documents with case report forms (CRFs) submitted to the sponsor.

b. **Determine** if, when, and by whom CRFs are verified against supporting documents (hospital records, office charts, laboratory reports, etc.) at the study site.

c. **Determine** if all CRFs are verified during monitoring visits. If a representative sample was selected, determine how the size and composition of the sample were selected.

d. **Determine** if a form is used for data verification and **obtain** a copy. **Obtain** a copy of any written procedures (SOPs and guidelines) for data verification.

e. **Determine** if the sponsor/CRO/monitor, or a data management company contracted by the sponsor/CRO, makes corrections to CRFs and if confirmation or verification from the clinical investigator is obtained when such changes are made.

f. **Determine** how the sponsor/CRO assures that IRB approval is obtained prior to the enrollment of subjects in the study.

g. **Determine** how the sponsor/CRO assures that informed consent is obtained from all subjects in the study.

h. If sponsor-generated, site-specific data tabulations are provided by the assigning Center, **compare** the tabulations with CRFs submitted by the clinical investigator.

H. QUALITY ASSURANCE (QA)

Clinical trial quality assurance units (QAUs) are not required by regulation. However, many sponsors obtain independent audits/data verifications to determine the sponsor's compliance with clinical trial SOPs and FDA regulations. These audits/data verifications may be conducted with or without the existence of an actual QAU. All QAUs and/or auditing personnel should be independent of, and separate from, routine monitoring or quality control functions. Findings that are the product of a written QA program will not be inspected without prior concurrence of the assigning FDA headquarters unit. Refer to Compliance Policy Guide 7151.02 for additional guidance in this matter.

1. **Determine** if the sponsor/CRO conducts QA inspections and audits.

2. If the sponsor/CRO has a QAU, **determine** how it is organized and operates.

3. **Obtain** a copy of any written procedures (SOPs and guidelines) for QA audits and the operation of any QAU.

4. D**escribe** the separation of functions between QA auditing and monitoring of clinical trials.

5. Sponsors of drug studies are required to submit a list of audited studies (21 CFR 314.50(d)(5)(xi)). If the assigning Center provides the list, compare the list with the sponsor's records.

I. SAFETY/ADVERSE EVENT REPORTING

1. A sponsor must notify FDA and participating investigators (in addition to reviewing IRBs for device studies) of the following types of information associated with the use of Investigational articles.

    a. Drugs/biologics 312.32(c) – IND safety reports of potential serious risks within 15 calendar days after the sponsor determines that the information qualifies for reporting; no later than 7 calendar days if unexpected fatal or life-threatening suspected adverse reaction; 312.32(d) follow-up reports as applicable.[15]

    b. Drugs in bioavailability and bioequivalence studies that are exempt from the IND requirements 320.31(d)(3) – Report any serious adverse event within 15 calendar days; if fatal or life-threatening, within 7 calendar days; follow-up reports as soon as information is available.

    c. Animal drugs 511.1(b)(8)(ii) – Promptly investigate and report any findings associated with the use of the new animal drug that may suggest significant hazards.

    d. Devices 812.150(b)(1) – Written report within 10 working days after the sponsor first receives notice of the unanticipated adverse device effect.

2. **Determine** if safety information/unanticipated adverse device effects were reported to FDA as required by regulations.

[15] Revised safety reporting regulations issued September 29, 2010, effective March 28, 2011, include new and revised definitions and new reporting requirements. See http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2010_register&docid=fr29se10-3.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf.

3. **Determine** if safety information/unanticipated adverse device effects were reported to participating investigators (and to reviewing IRBs for device studies) as required by the regulations.

4. **Review** the procedures (e.g., frequency, scope) the sponsor/CRO uses for the receipt, evaluation, and monitoring of safety information/unanticipated adverse device effects, as well as the process for updating the investigator brochure. If applicable, review the composition and function of the safety team/committee (for drugs and biologics).

Obtain copies of any notification to investigators relating to safety information/unanticipated adverse device effects.

J. DATA COLLECTION AND HANDLING

1. Study Tabulations

a. Sponsors are required to submit analyses of all clinical studies pertinent to the proposed drug/device use in any marketing application/submission (NDA/NADA/BLA/ PMA/510(k)) that is supported by clinical data (21 CFR 314.50(d)(5)(ii-iv), 514.1(b)(8), 601.25(b)(3), 814.20(b)(3) and 807.92(b)).

i. **Obtain** a list of all clinical studies contained in the application(s)/submission(s) referenced in the inspection assignment.

ii. **Identify** any pertinent studies not included in the marketing application/submission and **document** the reason they were not included.

2. Investigator Tabulations

a. Sponsors are required to obtain from each clinical investigator a signed agreement (Form FDA 1572 for human drugs and biologics and an investigator agreement for devices) prior to initiation of the clinical trial (21 CFR 312.53(c) and 812.43(c)).

i. **Review** all signed 1572s/agreements associated with the study(ies) specified in the assignment.

ii. **Identify** any clinical investigators with signed 1572s/agreements not included in the marketing application/submission and **document** the reason they were not included.

3. Data Tabulations

a. FDA regulations require that sponsors submit data tabulations on each subject in each clinical trial in an NDA/BLA/PMA (21 CFR 314.50(f)(1) and

814.20(b)(6)(ii)).

i. **Determine** if the number of subjects in the studies performed under an IND/IDE is the same as the number reported in the NDA/BLA/PMA.

a) **Determine** the number of subjects listed in each of the clinical trials and compare the number of subjects in the tabulations to the corresponding CRFs submitted to the sponsor.

b) **Document** any subjects not included in the NDA/BLA/PMA and the reason they were not included.

4. Data Collection and Handling Procedures

a. **Review** the sponsor's written procedures (SOPs and guidelines) to assure the integrity of safety and efficacy data collected from clinical investigators (domestic and international).

b. **Verify** that the procedures were followed and document any deviations.

K. RECORD RETENTION

Refer to 21 CFR 312.57(c), 511.1(b)(8)(i), and 812.140(d). **Verify** that the sponsor maintained required records (e.g., drug disposition, financial disclosure information from investigators) for the prescribed period of time.

L. FINANCIAL DISCLOSURE

1. **Determine** if the sponsor obtained financial disclosure information from each investigator before his/her participation in the clinical trial, as required by 21 CFR Part 54 and 21 CFR 312.53(c)(4) and 812.2(b)(5) and 812.43(c)(5).

2. **Determine** if the sponsor received prompt updates regarding relevant changes in financial disclosure information from investigators during the study and for one year after study completion.

3. **Determine** if the sponsor reported to FDA (on Form FDA 3454 and 3455, respectively), all pertinent investigator disclosures and certifications of financial information as required by 21 CFR 54.6.

4. **Determine** if the sponsor retained the documentation to support the certifications and disclosures of investigators' financial information that was reported to FDA.

M. ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

Computerized systems are commonly used in clinical investigations to create, modify, maintain, archive, retrieve, and/or transmit clinical data. Computerized systems range from isolated pieces of equipment that are used at a clinical site to collect/archive clinical data (e.g., a laptop) to complex integrated systems that consist of a variety of hardware, firmware, and software components that are located at multiple sites (e.g., a web-based system managed by an independent software vendor to which the sponsor and clinical sites have controlled access).

Regardless of the type of system used by the clinical site, an important principle to understand when evaluating clinical research data is that the regulatory requirements for the clinical data do not change whether clinical data are captured on paper, electronically, or using a hybrid approach. Data must be reliable and usable for evaluating the safety and/or effectiveness of FDA-regulated products.

Another important point is that the agency has stated in its guidance entitled, "Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application" (Part 11 Guidance) (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf) that only certain electronic records will be subject to 21 CFR Part 11 (Part 11), and that the agency intends to exercise enforcement discretion with regard to specific Part 11 requirements. Part 11 describes the technical and procedural requirements that must be met if a firm chooses to maintain records electronically and/or use electronic signatures. Part 11 is a companion regulation to other FDA regulations and laws. It is in these other regulations and laws, called "predicate rules," where specific requirements for issues such as recordkeeping, record content, signatures, and record retention are addressed.

Section III. B. 2 of the Part 11 Guidance states that Part 11 is applicable to the following electronic records and electronic signatures:

- Records that are required to be maintained under the predicate rules and that are maintained in electronic format *in place of paper format.*
- Records that are required to be maintained under the predicate rules, that are maintained in electronic format *in addition to paper format*, and *are relied on to perform regulated activities.*
- Records that are submitted to FDA, under predicate rules, and that are in electronic format.
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials or other general signings that are required by the predicate rules.

In Section III. C of the Part 11 Guidance, specific requirements for which the agency intends to exercise enforcement discretion include the:

- Validation of computerized systems;
- Use of computer-generated, time-stamped audit trails;
- Use of legacy systems;
- Generation of copies of records;
- Protection of records (i.e., record retention and availability)

The field investigator should consult with the Center contact for guidance on the depth to which Part 11 issues should be covered during an inspection. When assessing study compliance, any discrepancies

should be **documented** under the appropriate predicate rule requirement. Questions should be referred to the Center contact.

1. Scope of electronic records/electronic signatures

   a. **Determine** whether electronic records and/or electronic signatures are required by predicate rules, and/or are used in place of paper records (or relied upon to perform regulated activities) and handwritten signatures. If this is the case, requirements of Part 11, as interpreted by the Part 11 Guidance, apply. If this is not the case, Part 11 requirements do not apply, and the paper records should be evaluated for compliance with the applicable regulations.

   b. **Determine** whether electronic data and data collection methods are defined in the study protocol. **Describe** any computerized system(s) used at the study site(s) to generate, collect, or analyze data (e.g., stand alone personal computer, web-based system, hand-held computers).

   c. **Determine** how the sponsor/CRO has ensured that sites have access to their original electronic records and how this access is maintained for the required data retention period at a minimum.

2. Procedures

   a. **Determine** how the sponsor/CRO determines which records are used for regulatory purposes (e.g., if there is an SOP and if it is followed).

   b. **Determine** if the sponsor/CRO has established procedures to create, modify, maintain, or transmit electronic records, e.g., user manuals, operating instructions, access policies and procedures, training policies, or management controls.

   c. **Determine** if the sponsor/CRO has procedures to demonstrate that the computerized system was tested for its intended use (e.g., documentation of user acceptance testing).

   d. **Determine** how the sponsor/CRO documents that there are sufficient personnel with the necessary education, background, training, and experience to ensure that all protocol requirements that employ electronic systems are correctly performed.

   e. **Determine** if the sponsor/CRO has procedures for identifying training needs to ensure that all pertinent personnel (e.g., individuals who develop, maintain, and/or utilize computerized systems, including staff at the clinical sites) are trained to adequately perform their assigned responsibilities.

   f. **Determine** how the sponsor/CRO ensures that only authorized personnel have access to study data – e.g., if there is a log of authorized users for each clinical site; if all users – at the sites, sponsor, CRO, data processing center – have appropriate user IDs, passwords, and access privileges..

3. Data collection:

   a. **Describe** procedures for collection, retention, and transmission of data at each clinical site. That is, **determine** if there are file transfer protocols for electronic clinical data transmitted to and from the clinical site/sponsor/CRO/data processing center.

   b. **Determine** whether original data entries and changes can be made by anyone other than the clinical investigators.

   c. **Determine** how the electronic data were reviewed during monitoring visits. If any data monitoring was accomplished remotely, **determine** what was covered and **obtain** copies of any SOPs and/or documentation of such reviews.

4. Security

   a. **Determine** who is authorized to access the system.

   b. **Describe** how the computerized systems are accessed (e.g., password protected, access privileges, user identification).

   c. **Determine** how information is captured related to the creation, modification, or deletion of electronic records (e.g., audit trails, date/time stamps).

   d. **Describe** whether there is backup, disaster recovery, and/or contingency plans to protect against data loss. Were there any software upgrades, security or performance patches, or new instrumentation during the clinical trial? Could the data have been affected?

   e. **Describe** how error messages or system failures were reported to the sponsor, CRO, or study site and the corrective actions, if any, which were taken.

   f. **Determine** how the system and data were handled during site closure.

N. TEST ARTICLE

1. Integrity

   Describe the sponsor's procedures to ensure the integrity of the test article from manufacturing to receipt by the clinical investigator:

   a. **Determine** if the test article met required release specifications. For drugs, review the Certificate of Analysis, if available. For biologics, review the Certificate of Analysis, where appropriate and available, and/or the lot release documentation.

   b. **Determine** if the test article is not in its final form and requires preparation, manipulation, or processing by the clinical protocol and/or manufacturer's instructions (e.g., mixing plasma with bone chips immediately before use or manipulation of a study subject's cell or tissue specimen) prior to receipt by the subject.

   c. **Determine** where the test article was stored and if the conditions of storage were appropriate.

d. **Determine** how the sponsor verified test article integrity during shipment to the clinical study sites.

e. **Determine** if the test article was properly labeled (See 21 CFR 312.6, 511.1(b)(1), and 812.5).

f. **Determine** if the test article was recalled, withdrawn, or returned.

2. Accountability

a. **Determine** whether the sponsor maintains accounting records for use of the test article including:

i. Names and addresses of clinical investigators receiving test articles. See 21 CFR 312.57, 511.1(b)(3), and 812.140(b)(2).

ii. Shipment date(s), quantity, batch or code mark, or other identification number of test article shipped. See regulations above.

iii. Final disposition of the test article. See 21 CFR 312.59, 511.1(b)(7)(ii), and 812.140(b)(2).

iv. For animal drug products, final disposition of food-producing animals treated with the test article (21 CFR 511.1(b)(5)).

A detailed audit should be performed when serious violations are suspected.

b. **Determine** whether the sponsor's records are sufficient to reconcile test article usage (compare the amount shipped to the investigators to the amount used and returned or disposed of).

c. **Determine** whether the clinical investigator appropriately documented any manipulation or processing of the test article and, if the investigator did manipulate or process the test article, **verify** that all relevant requirements set forth in the protocol were met and fully documented.

d. **Determine** whether all unused or reusable supplies of the test article were returned to the sponsor when either the investigator(s) discontinued or completed participation in the clinical investigation, or the investigation was terminated.

e. If the test article was not returned to the sponsor, **describe** the method of disposition and **determine** if adequate records were maintained.

f. For device studies, **determine** how the sponsor controls and monitors the use of devices that are not single-use products, such as lithotripters or excimer lasers.

g. **Determine** if the sponsor is charging for the test article and **document** the fees charged.

O. DEVICES

1. Requests for inspections from the Center for Devices and Radiological Health (CDRH) generally involve Significant Risk (SR) device studies that require full compliance with the Investigational Device Exemption (IDE) regulations at 21 CFR 812. In addition to covering the identified SR device study, the investigator should **determine** whether the sponsor/CRO/monitor is involved in Non-significant Risk (NSR) device studies which require compliance with the abbreviated IDE requirements at 21 CFR 812.2(b). The abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion, including compliance with 21 CFR 812.5, 812.7, 812.46. 812.140(a)(3)(i), and (b)(4) and (5), 812.150(b)(1) through (3) and (5) through (10). NSR device studies do not have to have an IDE application approved by FDA.

   When appropriate, the investigator should choose at least one (1), but no more than three (3), NSR device investigations to **determine** the level of compliance with the abbreviated requirements.

2. Humanitarian Use Devices (HUDs) and Humanitarian Device Exemptions (HDEs) (see also the guidance document on the Humanitarian Device Exemption (HDE) Regulation: Questions and Answers, available at (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm)

   As defined in 21 CFR 814.3(n), a HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. An HDE is an application similar to a premarket approval (PMA) application, but is exempt from the reasonable assurance of effectiveness standard. HDE approval is based, in part, on evidence that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit from use of the device outweighs the risk of injury or illness. This decision must take into account the probable risk and benefits of currently available devices and alternative forms of treatment. FDA approval of an HDE authorizes an applicant to market a HUD, subject to certain profit and use restrictions. Specifically, HUDs cannot be sold for profit, except in narrow circumstances[16], and they can only be used in a facility after an IRB has approved their use in that facility, except in certain emergencies.

[16] See Title III – Pediatric Medical Device Safety and Improvement Act of 2007 – in the medical device provisions of the Food and Drug Administration Amendments Act (FDAAA) of 2007 available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/UCM109100.pdf.

There is a distinction between "use" of a HUD and "investigational use/clinical investigation" of a HUD.

a. Prior to approval of a HDE application, any studies using the device must be conducted in compliance with the applicable IDE regulations (21 CFR Part 812). **Determine** if the sponsor is conducting any such studies. If so, **verify** that the study, if it is considered a significant risk device study, is conducted under an IDE – i.e., has IDE approval from FDA as well as IRB approval, or IRB approval with concurrence that it is a non-significant risk device study, or is exempt from IDE requirements under 21 CFR 812.2(c).

b. "Use" of a HUD that has an approved HDE, requires IRB approval before use in a facility, with the exception of emergency use (21 CFR 814.124). The HDE holder is responsible for maintaining records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with the reviewing IRBs, and any other information required by the reviewing IRB or FDA (21 CFR 814.126(b)(2)). In addition, the HDE holder is subject to certain reporting requirements (21 CFR 814.126(b)(1)), including monitoring how many devices are distributed each year and periodically providing FDA with updated information, including information to demonstrate that the HUD designation is still valid. **Determine** if the sponsor holds any approved HDEs. If so, **verify** that there is documentation that all facilities using the HUD have the approval from an appropriate IRB; that required records are maintained, including those related to device distribution; and that periodic updates have been submitted to FDA.

c. An HDE holder may collect safety and effectiveness data in a clinical investigation for the HDE-approved indication(s) without an IDE. As long as the HUD is being studied in accordance with the approved indication(s) described in the labeling, the HUD is legally marketed and can be lawfully shipped without an IDE. IRB approval (21 CFR 56) and informed consent of the subjects (21 CFR 50) are still required for these studies. **Determine** if the sponsor is conducting such a clinical investigation. If so, **verify** that the study is being conducted in compliance with 21 CFR Parts 50 and 56.

d. Clinical investigations of a HUD for an indication different from the HDE-approved indication(s) must be conducted in compliance with the applicable IDE regulations (21 CFR 812), in addition to complying with the requirements for IRB approval and informed consent. If the study is a significant risk study, an FDA-approved IDE is required (21 CFR 812.2). **Determine** if the sponsor is conducting a study of a HUD for a different indication than the HDE-approved indication. If so, **verify** that the study is being conducted in compliance with 21 CFR Parts 812, 50, and 56.

P. EMERGENCY RESEARCH

1. **Determine** if the sponsor/CRO is conducting or has conducted any "emergency research" studies, i.e., studies described in 21 CFR 50.24, which specifies circumstances in which an IRB may approve an investigation without requiring that informed consent be obtained from research subjects. If so:

    a. **Determine** if the sponsor consulted with representatives of the communities in which the investigation is conducted and from which subjects are drawn, as required by 21 CFR 50.24(a)(7)(i).

    b. **Determine** if the sponsor provided public disclosure to the communities in which the investigation is conducted both prior to and following completion of the investigation, as required by 21 CFR 50.24(a)(7)(ii) and (iii).

    c. **Determine** if the sponsor promptly submitted copies of the required public disclosures to the Division of Dockets Management as required by 21 CFR 312.54(a) and 812.47(a).

    d. **Determine** if the sponsor established an independent data monitoring committee to exercise oversight of the investigation, as required by 21 CFR 50.24(a)(7)(iv).

    e. **Determine** if the sponsor received any determination from an IRB that the IRB could not approve an emergency research study under 21 CFR 50.24. If so, did the sponsor promptly provide this information in writing to FDA, the sponsor's clinical investigators who are participating or asked to participate in the same or a substantially equivalent clinical investigation of the sponsor, and other IRBs that have been or are asked to review this or a substantially equivalent investigation by that sponsor (as required by 21 CFR 50.24(e))? (See 21 CFR 312.54(b) and 812.47(b).)

Q. INTERNATIONAL DATA – HUMAN DRUGS AND BIOLOGICS

Sponsors are not required to conduct non-U.S. clinical trials under an IND, but often submit data from international study sites to FDA in support of marketing or research applications. In 2008, FDA revised its criteria for accepting non-IND, non-U.S. clinical studies as support for an IND or a new drug application (NDA). See 21 CFR 312.120 (accessible from http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm). This revised section of the regulation became effective October 27, 2008.

FDA's requirements for accepting such studies are as follows:

- The study must be conducted in accordance with Good Clinical Practice (GCP), which 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 also 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 the subject's legally authorized representative if the subject is unable to provide consent) before initiating a study.

- FDA is able to validate the data from the study through an on-site inspection if the agency deems it necessary.

A sponsor or applicant is required to submit the following information for non-IND non-U.S. clinical trials to FDA that support an IND or application for marketing approval:

a. The investigator's qualifications;
b. A description of the research facilities;
c. A detailed summary of the protocol and study results, and if we request them, case records or additional background data;
d. A description of the drug substance and drug product, including components, formulation, specifications, and, if available, the bioavailability of the drug product;
e. Information showing that the study is adequate and well-controlled (if the study is intended to support the effectiveness of the product);
f. The name and address of the independent ethics committee (IEC) that reviewed the study and a statement that the IEC meets the definition in 21 CFR 312.3;[17]

[17] 21 CFR 312.3(b) defines "independent ethics committee" (IEC) as "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."

g. A summary of the IEC's decision to approve or modify and approve the study or to provide a favorable opinion;
h. A description of how informed consent was obtained;
i. A description of what incentives, if any, were provided to subjects to participate;
j. A description of how the sponsors monitored the study and ensured that the study was consistent with the protocol; and
k. A description of how investigators were trained to comply with GCP 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 commitments must be maintained and available for agency review).

If the study identified for inspection includes non-IND, non-U.S. site(s), the sponsor should have records related to the information listed above. **Consult** with the Center contact about the need to **review** and/or **obtain** copies of these records.

R. NONCLINICAL LABORATORY STUDIES

ONE OR MORE OF THE FOLLOWING ARE ONLY APPLICABLE WHEN SPECIFICALLY REQUESTED IN THE INSPECTION ASSIGNMENT

1. **Determine** if the sponsor conducted or contracted for nonclinical studies related to the product that is the subject of the clinical study(ies) specified in the assignment – i.e., studies subject to 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. If so, **collect** copies of information documenting where and when the nonclinical studies were conducted. For contracted studies, **collect** copies of the agreement with the contracted party.

2. Sponsors are required to provide a statement in applications/submissions to FDA that nonclinical studies were conducted in compliance with 21 CFR Part 58 or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for noncompliance. This statement must appear in the Notice of Claimed Investigational Exemption for New Animal Drug studies, IND and IDE applications, and marketing applications/submissions (for devices this statement must appear in a PMA) (21 CFR 312.23(a)(8)(iii), 314.50(d)(2)(v), 314.125(b)(15), 511.1(b)(4)(ii), 514.1(b)(12)(iii), 601.2(a), 812.27(b)(3), 814.20(b)(6)(i)). **Collect** copies of documentation used to support a sponsor's statement that the studies were GLP compliant or the rationale as to why the studies were not conducted in compliance with the regulation.

3. **Determine** if the sponsor approved the nonclinical study protocol(s). **Collect** any available documentation.

4. The regulation requires that specific information pertinent to test and control article characterization is available either before study initiation or concomitantly (21 CFR 58.105). This includes: stability testing; documentation for each batch of the identity, strength, purity, and composition or other characterization that defines the article; and documentation of methods of synthesis, fabrication, or derivation. **Determine** whether the sponsor or the test facility was responsible for meeting these requirements. **Collect** documentation regarding where and when the testing was conducted as well as copies of any resulting reports.

5. **Determine** where nonclinical studies data and records are retained and **collect** the name and address of that location. The test facility is required to retain, with a few specified exceptions, all raw data, protocols, final reports and specimens as specified in 21 CFR 58.195(b). If the test facility goes out of business during the required records retention period, the regulation requires that all data and records required to be retained be transferred to the sponsor's archives and that FDA be informed of this transfer (21 CFR 58.195(h)). If such a transfer occurred, **determine** the location of the sponsor's archives and **collect** documentation that FDA has been notified of the transfer.

S. SAMPLE COLLECTION

1. Samples may be obtained at the direction of the assigning Center.

2. During the inspection, if collection appears warranted, contact the assigning Center for further instructions.

T. ESTABLISHMENT INSPECTION REPORTS (EIRs)

If the inspection assignment resulted from FDA's receipt of a marketing application/submission, information contained in the EIR may be used in support of marketing approval or denial. If the inspection was assigned "for cause" or as part of general surveillance, information contained in the EIR may be used to determine if the ongoing study should be allowed to continue, either in its entirety or at specific sites. Therefore, the EIR must **document** all findings that could significantly impact the decision-making process.

1. Standard Narrative Report

    a. A standard narrative report will be prepared and submitted in the following situations:

        i. The initial inspection of a firm;

        ii. All inspections for which the field recommends an Official Action Indicated (OAI) classification; and

        iii. Any assignment specifically requesting a standard narrative report.

    b. Refer to IOM 5.10.4, Narrative Report. Individual sections that are relevant to a BIMO standard narrative report include: Summary; Administrative Data; History; Individual Responsibility and Persons Interviewed; Objectionable Conditions and Management's Response; Supporting Evidence and Relevance; Discussion with Management; Refusals; General Discussion with Management; Additional Information; Voluntary Corrections; Exhibits Collected; Attachments; and Signature. See also, IOM 5.2.9: Interviewing Confidential Informants.

c. In addition to these, include the appropriate headings outlined in Part III of this Compliance Program (Sections III. C through Q). The report must include sufficient information and documentation to support the recommended classification.

2. Summary of Findings Report

a. A Summary of Findings Report may be submitted for non-violative inspections of sponsors/CROs/monitors who have previously been inspected. A full inspection must be conducted even if a Summary of Findings Report is appropriate, i.e., an abbreviated inspection is not justified. A Summary of Findings report must contain sufficient narrative and accompanying documentation to support the inspectional observations. The specific headings appearing under Part III. Inspection Procedures should be fully addressed during the inspection, as appropriate to the inspection assignment. In addition, the EIR should be clearly identified as a Summary of Findings Report.

b. The report should include all of the headings described in IOM section 5.10.4.1, Narrative Reports for Non-Violative Establishments:

i. Reason for inspection;

ii. Date, classification, and findings of the previous inspection;

iii. The inclusive dates of the inspection;

iv. Name of the person to whom credentials were shown and the Notice of Inspection was issued and the person's authority to receive the Notice;

v. Scope of the inspection, including:

a) Updated history of business;

b) Administrative procedures;

c) Persons interviewed and individual responsibilities;

d) Protocol title, protocol number, and the FDA research (IND, IDE, INAD) or marketing (NDA, NADA, BLA, PMA, 510(k)) application numbers;

e) Areas covered during the inspection including but not limited to SOPs relevant to the study, test article accountability, monitoring reports, actions taken to secure site compliance when necessary, IRB approvals, adverse event reporting, special instructions or directives (if provided in the assignment);

vi. Significant observations, if any;

vii. Statement of the close-out discussion and the sponsor's/CRO's/monitor's response(s) or correction(s)

a) Discussion of inspectional observations, including observations noted on the 483;

b) 483 observations should be referenced in the EIR; documentation of the observations should be included as exhibits;

c) Response to the 483 observations – attach any response to the EIR if provided by the sponsor/CRO/monitor prior to submission to the Center;

viii. FDA investigator's handwritten signature, and signature(s) of other members of the inspection team, if applicable.

PART IV - ANALYTICAL

Centers will provide specific instructions if sample analysis of investigational products is needed (e.g., complaint investigation or for-cause inspection of an ongoing study). Contact the Center for additional guidance. [See also III. Inspectional, R. Sample Collection.]

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A. ADMINISTRATIVE

1. District EIR Classification Authority

   The District is encouraged to review and initially classify EIRs under this Compliance Program as outlined in item 3 below.

2. Center EIR Classification Authority

   The Center has final classification authority for all EIRs generated under this Compliance Program. If the Center is considering a classification that differs from the District's recommended classification, the Center will contact the District to discuss the issues (see Part II B. 3. c) as soon as possible to avoid delays in the final classification process. In addition, the Center will provide the District with notice of all final classifications, including the rationale for any that differ from the District's initial classification.

3. EIR Classifications

   The following guidance is to be used in conjunction with the instructions in FMD-86[18] for initial District and Center classification of EIRs generated under this Compliance Program:

   a. NAI – No Action Indicated. No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action);

   b. VAI – Voluntary Action Indicated. Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action; and

   c. OAI – Official Action Indicated. Regulatory and/or administrative actions will be recommended.

4. Administrative/Civil/Criminal Actions will be in accordance with 21 CFR Parts 312, 511, and 812. FDA may invoke other legal sanctions under the FFDCA or Title 18 of the United States Code where appropriate.

   a. Administrative Actions. The following administrative actions are available:

      i. Untitled Letters

      ii. Warning Letters

      iii. Reinspection to verify promised corrective actions

      iv. Regulatory meetings

[18] See http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm061430.htm.

v. For a study subject to 21 CFR Part 312, placing a clinical hold on the study (21 CFR 312.42)

vi. If the inspection involves a study subject to 21 CFR Part 812, withdrawal of approval of the IDE application (21 CFR 812.30(b))

vii. If the inspection involves a study subject to 21 CFR Part 511, termination of the exemption

viii. Refusal to approve or license

ix. Withdrawal of approval (PMA, NDA, NADA)

x. Determination of not substantially equivalent (21 CFR 807.100(a)(2)) or rescission of a 510(k) (see 21 CFR 10.33 and 10.75) for devices

xi. Implementation of the Application Integrity Policy

xii. For Sponsor-Investigators, additional administrative/enforcement actions that may be applicable are described in the Compliance Program Guidance Manual for Clinical Investigators and Sponsor-Investigators (CPGM 7348.811), as referenced in Part I - Background above.

b. Civil/Criminal Actions. The following actions are available:

i. Seizure of test articles

ii. Injunction

iii. Prosecution under the FFDCA and other Federal statutes, i.e., 18 U.S.C. 2, 371, 1001, and 1341

iv. Referral of pertinent matters with headquarters' concurrence to other Federal, state, and local agencies for such action as that agency deems appropriate.

B. REGULATORY

The following criteria are relevant to FDA's classification of inspections of sponsors/CROs/monitors:

No Action Indicated (NAI). No objectionable conditions or practices (e.g., violations of 21 CFR Parts 50, 54, 56, 58, 312, 511, 812) were found during the inspection, or the significance of the documented objectionable conditions found does not justify further FDA action.

Any post-inspectional correspondence acknowledges the sponsor's/CRO's/monitor's basic compliance with pertinent regulations.

Voluntary Action Indicated (VAI). Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any further regulatory (advisory, administrative, or judicial) action because the objectionable conditions do not meet the threshold for regulatory action (i.e., regulatory violations uncovered during the inspection are few and do not seriously impact subject safety

or data integrity).

Post-inspectional correspondence may identify the issues and, when needed, state that FDA expects prompt, voluntary corrective action by the sponsor/CRO/monitor.

Official Action Indicated (OAI). An OAI recommendation is appropriate when regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violation(s) support a finding that:

a) Subjects participating in studies conducted by the sponsor/CRO or overseen by the monitor would be or have been exposed to an unreasonable and significant risk of illness or injury; OR
b) Subjects' rights would be or have been seriously compromised; OR
c) Data integrity or reliability is or has been compromised.

Post-inspectional correspondence would usually be a Warning Letter (WL). Implementation of the agency's Application Integrity Policy (AIP) is also possible. AIP may be considered when there is evidence of a pattern or practice of wrongful conduct that raises a significant question about the reliability of data in studies conducted to support an application(s) for marketing. (See information regarding AIP at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm.)

The Centers may rely on information from inspections of CROs and/or monitors that were contracted to assume some or all sponsor responsibilities, as well as information from inspected study sites, to determine whether the sponsor/CRO/monitor is compliant. If an OAI decision is reached, additional information (e.g., previous inspectional findings, correspondence, or other information about the sponsor/CRO/monitor) may assist the Center in preparing appropriate post-inspectional correspondence. If the Center believes that the violations can be corrected through specific action(s) by the sponsor/CRO/monitor (e.g., preparation of, and compliance with, a detailed corrective action plan that is acceptable to FDA) and adherence to the corrective action plan has a high probability of preventing similar or other violations from occurring in the future, the Center may choose to issue a WL. Nevertheless, the Center should be prepared to take further action if the sponsor/CRO/monitor does not respond appropriately (i.e., fails to respond, fails to develop an adequate corrective action plan, or is found, during a subsequent inspection, to have failed to comply with a corrective action plan.)

When applying the classification criteria, Center reviewers will evaluate the impact of the sponsor's deficiencies on the general conduct of their clinical trials, with particular attention to the safety, rights, and welfare of study subjects and the integrity of the resulting data. The following are intended to serve as examples of violations that, alone or in combination, would be considered significant and may warrant OAI classification. This list is not all inclusive and other circumstances may also merit OAI classification. Each example can have gradations in severity and the specific observation(s) should support the seriousness of the violation(s) and its impact on subject protection and/or data integrity.

Violation/Related Citation	Examples/supporting evidence
Lack of a signed 1572/investigator agreement for one or more clinical sites 21 CFR 312.53(c)(1) 812.43(c)	Evidenced by absence of required documentation.
Failure to select qualified clinical investigators 21CFR 312.53(a), 312.53(c)(1)(iii) and (iv) 812.43(a), 812.20(b)(7)	Monitoring reports, Form FDA 1572s, and/or investigator agreements indicate that one or more clinical investigators did not have appropriate training and/or experience to perform their responsibilities in the study. Monitoring reports, Form FDA 1572s, and/or investigator agreements indicate that one or more clinical investigators did not have access to the facilities necessary to conduct the study.
Failure to select qualified monitors 21 CFR 312.53(d) 511.1(b)(8)(ii) 812.43(d)	Non-compliance and/or data issues evidenced at study sites were not discovered by the study monitor and/or included in monitoring reports. One or more sites were not trained to properly conduct the study (for example, required QC tests were not performed). There is no documentation that one or more study monitors had clinical trial experience.
Lack of a required IND/IDE or failure to submit a "Notice of Claimed Investigational Exemption for a New Animal Drug" 21 CFR 312.20 812.20 511.1(b)(4)	**NOTE:** This citation requires consultation with the Center for a definitive conclusion before inclusion on a 483
Failure to provide investigators with the information they need to conduct the investigation.	The sponsor failed to provide one or more investigators with the study brochure and/or other information pertinent to the

21 CFR 312.50, 312.55 812.40, 812.45	conduct of the study prior to initiation of the study at the site(s) in question. Significant new adverse effects or risks were reported by the investigators to the sponsor, but the sponsor failed to promptly report them to all investigators. The sponsor misrepresented the correct IDE/IND status of the study to one or more investigators.
Failure to ensure that IRB approval was obtained. 21 CFR 312.53(c)(v) 812.40, 812.42	The investigation was initiated at one or more sites prior to or without sponsor receipt of evidence of IRB approval for the site(s) in question.
Failure to notify FDA of all investigators participating in the study. 21 CFR 312.23(a)(6)(iii)(b), 312.30(c) 511.1(b)(4)(iii) 514.1(b)(8)(vi) 812.20(b)(4), 812.150 (b)(4) 814.20(b)(6)(ii)	One or more investigators who participated in the study were not included in the initial IND/IDE application, the Notice of Claimed Investigational Exemption for a New Animal Drug, required study updates, and/or the marketing application/submission.
Failure to obtain required financial disclosure information prior to a clinical investigator's participation in the study 21 CFR 312.53(c)(4) 812.43(c)(5)	Dates on financial disclosure reports from one or more study investigators are after their initial participation in the study. Lack of financial disclosure information from one or more investigators participating in the study.
Failure to adequately monitor the study 21 CFR 312.50, 312.53(d), 312.56(a) 511.1(b)(8)(ii)* 812.40, 812.43(d), 812.46 *Specific language differs: "provide for current monitoring"	One or more study sites had significant protocol deviations, informed consent violations, IRB reporting violations, and/or discrepancies that were not documented during monitoring, or monitoring reports were inaccurate. Correspondence between the sponsor and one or more sites noted ongoing noncompliance with completion, review,

	and/or submission of CRFs, but monitoring reports did not include information regarding CRF issues or were inaccurate or inconsistent. The sponsor did not conduct or arrange for monitoring activities. The sponsor, monitor, or CRO instructed one or more sites to violate the protocol or instituted ad hoc protocol changes without IRB approval or notifying FDA.
Failure to bring non-compliant investigators into compliance 21 CFR 312.56(b) 812.46(a)	The sponsor failed to take action to correct continuing significant noncompliance documented in monitoring or other reports.
Failure to maintain or inadequate accountability for the investigational product 21 CFR 312.57(a), 312.59 511.1(b)(3), 511.1(b)(7) 812.43(b), 812.140(b)(2)	No or inadequate records of distribution and/or retrieval or disposition of the investigational product. Investigational product was shipped to individuals for whom the sponsor lacks a signed 1572 (for drug and biologics studies) or a signed investigator agreement (for device studies) or who were not named in the Notice of Claimed Investigational Exemption for a New Animal Drug.
Failure to report adverse events 21 CFR 312.50, 312.56(c)[references 312.32] 314.50(d)(5)(vi)(*a*) 511.1(b)(8)(ii) 514.1(b)(8)(iv) 807.92(b)(2) 812.46(b) 812.150(b)(1) 814.20(b)(6)(ii)	Evidence of adverse events reported by sites but not included in the marketing application/submission; lack of evidence for submission of adverse events reports for ongoing studies.

C. FOLLOW-UP INSPECTIONS

1. Centers should evaluate whether the violations found indicate systemic problems with the conduct of the study or the reliability of the data and whether additional inspection assignments should be issued (e.g., clinical investigators participating in the study(s) or IRBs).

2. Following issuance of a Warning Letter, Centers should be alert to information indicating that a Warning Letter recipient is the sponsor/CRO/monitor responsible for the conduct of other clinical investigations. If such information becomes available, the Center should schedule follow-up inspections to verify if the sponsor/CRO/monitor is fulfilling the terms of any corrective action plans and in compliance with applicable GCP regulations.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES

1. FDA laws

   Federal Food Drug and Cosmetic Act (FFDCA) – Sections 501(i), 505(i), 505(k)(2), 510(k), 513(f), 515, 520(g), and 520(m)

2. Most Relevant 21 CFR Regulations

   Part 50 Protection of Human Subjects
   Part 56 Institutional Review Boards
   Part 312 Investigational New Drug Application
   Part 511 New Animal Drugs for Investigational Use
   Part 812 Investigational Device Exemptions

3. Other 21 CFR Regulations

   Part 11 Electronic Records; Electronic Signatures,
   Part 54 Financial Disclosure by Clinical Investigators
   Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies (when applicable)
   Part 314 Applications for FDA Approval to Market a New Drug or Antibiotic Drug
   Part 514 New Animal Drug Applications
   Part 601 Licensing (Applications for FDA Approval of a Biologic License)
   Part 807 Premarket Notification Procedures (Subpart E)
   Part 814 Premarket Approval of Medical Devices (includes HDE requirements in 814.100)

4. SPECIFIC FORMS

   a. Form FDA 1571 – Investigational New Drug Application (See 21 CFR 312.23(a)(1)) (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf)

   b. Form FDA 1572 – Statement of Investigator (See 21 CFR 312.53(c)(1)) (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf)

   c. Form FDA 3454 – Certification: Financial Interests and Arrangements of Clinical Investigators (See 21 CFR 54.4(a)(1)) (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048304.pdf)

d. Form FDA 3455 – Disclosure: Financial Interests and Arrangements of Clinical Investigators (See 21 CFR 54.4(a)(3)) (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048310.pdf)

e. Form FDA 3458 – Notice of Claimed Investigational Exemption for a New Animal Drug (See 21 CFR 511.1(b)(4)) (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM052356.pdf)

5. FDA Guidelines, Guidances, and Inspection Guides

FDA Information Sheet Guidances for Institutional Review Boards, Clinical Investigators, and Sponsors (https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm)

Guidance for Industry: International Conference on Harmonization (ICH) E6, Good Clinical Practice: Consolidated Guidance (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf)

Guidance for Industry: Computerized Systems Used in Clinical Investigations (https://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf)

Guidance for Industry: Part 11: Electronic Records, Electronic Signatures-- Scope and Application (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf)

Guidance for Industry: Financial Disclosure by Clinical Investigators (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf)

General Principles of Software Validation; Final Guidance for Industry and FDA Staff (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm)

Investigations Operations Manual (IOM), Sections 5.3.8.3 (Filmed or Electronic Records) and 5.3.8.4 (Requesting and Working with Computerized Complaint and Data Failure) (https://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf)

Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects (https://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf)

Guidance for Industry (Guidance 85): Veterinary International Conference on Harmonization (VICH) GL9, Good Clinical Practice, Final Guidance (https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052417.pdf)

Compliance Policy Guide # 7150.09, Sec. 120.100: Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities
(https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073837.htm)

Compliance Policy Guide # 7151.02, Sec. 130.300: FDA Access to Results of Quality Assurance Program Audits and Inspection
(https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073841.htm)

Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff – Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of the Public Health Service Act, Added by Title VIII of the Food and Drug Administration Amendments Act of 2007
(https://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm)

Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
(https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf)

B. PROGRAM CONTACTS

1. When medical, technical or scientific questions or issues arise about a specific assignment or if additional information is required about a specific assignment, consult the Center contact identified in the assignment.

2. For operational questions, contact:

Office Regulatory Affairs (ORA)
ORAHQ BIMO Inspection POC@fda.hhs.gov

3. For questions about GCP and Compliance program issues, specific to a Center product area, contact:

Center for Drug Evaluation and Research (CDER)
Office of Scientific Investigations:
301-796-3150, FAX 301-847-8748

Center for Biologics Evaluation and Research (CBER)
Bioresearch Monitoring Branch:
240-402-9161, FAX 301-595-1304
Email: CBERBIMONotification@fda.hhs.gov

Center for Veterinary Medicine (CVM)
Premarket Compliance and Administrative Actions Team
240-402-5637, FAX 240-276-9241

Center for Devices and Radiological Health (CDRH)
Division of Bioresearch Monitoring:
301-796-5490, FAX 301-847-8137

Center for Food Safety and Applied Nutrition (CFSAN)
Division of Petition Review, CFSAN BIMO Program Manager
Yuguang Wang, HFS-003240-402-1757, FAX 301-436-2668

Center for Tobacco Products (CTP)
Office of Compliance and Enforcement (OCE) 1-877-287-1373

4. For crosscutting questions about Good Clinical Practice (GCP) policy and program issues impacting the Agency's BIMO Programs, or suggestions to improve this Compliance Program, contact:

Office of Good Clinical Practice
Office of the Commissioner
301-796-8340, FAX 301-847-8640

5. For information about inspection warrants and final issuance of Notice of Opportunity of Hearing (NOOH) letters for clinical investigator disqualifications, contact:

Office of Regulatory Affairs
Office of Enforcement and Import Operations (OEIO)
Division of Enforcement (DE)
301-796-8200, FAX 301-847-8635

PART VII – HEADQUARTERS RESPONSIBILITIES

A. CENTERS

Each Center:

1. Identifies the sponsor/CRO/monitor to be inspected (from applications for investigational exemptions and information in research or marketing permits), and forwards inspection assignments and background data (e.g., protocols, correspondence and Center concerns) to the field.

2. Reviews and makes final classifications of EIRs, and enters the classification into FACTS.

3. Conducts follow-up regulatory/administrative actions. Promptly provides copies of all relevant correspondence between the sponsor/CRO/monitor and FDA to the field offices.

4. Provides expert technical guidance, advice, information, interpretation, analysis, and support related to implementation of the clinical BIMO Program for internal and external constituents.

B. OFFICE OF REGULATORY AFFAIRS

1. Provides inspection quality assurance, training of field personnel, and operational guidance.

2. Maintains liaison with Centers and Field Offices and resolves operational questions

3. Coordinates and schedules joint Center and multi-District inspections, and international inspections.

G. OFFICE OF GOOD CLINICAL PRACTICE, OC

1. Coordinates crosscutting clinical BIMO Program activities, including modifications of this Compliance Program.

2. Provides expert technical guidance, advice, information, interpretation, and analysis relevant to clinical BIMO Program implementation to internal and external program constituents to assure program consistency.

3. Serves as Agency liaison to other Federal Agencies (e.g., OHRP, VA) for coordination of clinical BIMO and human subject protection issues.