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Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

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**U.S. Department of Health and Human Services
Food and Drug Administration**

Center for Devices and Radiological Health

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Preface

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction and Scope

FDA is issuing this guidance to clarify how we evaluate real-world data to determine whether they are sufficient for generating the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices. This guidance is applicable to all devices, as that term is defined under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), including software that meets the definition of a device.

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, and administrative and healthcare claims databases) can be used as data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

Real-World Evidence (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

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Under the right conditions, data derived from real world sources can be used to support regulatory decisions. RWD and associated RWE may constitute valid scientific evidence depending on the characteristics of the data. This guidance should not be construed to alter, or change in any way, the existing evidentiary standards applicable to FDA's regulatory decision-making; rather, it describes the circumstances under which RWD may be used to support a variety of FDA decisions based on the existing evidentiary standards. While FDA encourages the use of relevant and reliable RWD, this guidance neither mandates its use nor restricts other means of providing evidence to support regulatory decision-making. This guidance highlights some of the potential uses of RWD, and describes the factors that FDA considers when evaluating whether specific RWD is of sufficient quality to inform or support a regulatory decision. It also clarifies when an Investigational Device Exemption (IDE) may be needed to prospectively collect and use RWD for purposes of determining the safety and effectiveness of a device.

This document does not address the use of non-clinical data, adverse event reports, secondary use of clinical trial data (e.g., post hoc analyses), or systematic literature reviews. Nor does it address study design/conduct or analytical methodologies. While it does describe the factors that FDA considers when evaluating RWD or RWE, it does not provide a specific set of pass/fail criteria or other scoring tools for making a determination about the suitability of RWD or RWE for a particular regulatory decision.

This guidance does not affect any federal, state or local laws or regulations, or foreign laws or regulations that may be applicable to the use or collection of RWD, or that provide protections for human subjects (including informed consent requirements) or patient privacy. This guidance should be used to complement, but not supersede, other device-specific and good clinical practice guidance documents.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

To protect and promote the public health, FDA needs to understand and evaluate the available evidence related to regulated products.¹ For medical devices, available evidence is traditionally comprised of non-clinical and, in some cases, clinical studies conducted and provided to FDA by the device manufacturer or sponsor. However, FDA recognizes that a wealth of RWD covering medical device experience exists and is routinely collected in the course of treatment and management of patients. Data collected during clinical care or in the home setting may not have the same quality controls as data collected within a clinical trial setting. Even so, under certain

¹ FDA's What We Do (<http://www.fda.gov/AboutFDA/WhatWeDo/default.htm>).

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circumstances RWD may be of sufficient quality to help inform or augment FDA's understanding of the benefit-risk profile of devices at various points in their life cycle. RWD, which are typically collected for non-regulatory purposes in EHRs, registries, and administrative and claims data, may provide new insights into the performance and clinical outcomes associated with medical device use. This information can potentially be used by sponsors to demonstrate compliance with regulatory requirements and to aid FDA in our regulatory decision-making.

FDA has issued guidance documents on premarket and postmarket data collection,² benefit-risk determinations,³ patient preference information,⁴ and expedited access to medical devices for unmet medical needs in order to streamline the process for bringing new technologies to market while maintaining the assessment of reasonable assurance of safety and effectiveness of medical devices. FDA has also issued plans for, and has begun implementation of, the National Evaluation System for health Technology (NEST)^{5,6,7,8} to leverage RWD in order to more quickly identify safety problems and to better understand the benefit-risk profile of devices used in clinical care. FDA believes that, if leveraged correctly, the NEST may also help to reduce the time and cost of generating the types of evidence used to support the marketing authorization of FDA-regulated products and to meet postmarket study and reporting requirements.

Devices are often used in routine clinical practice for uses that are not within their cleared or approved indications for use. However, the knowledge gained from all uses of a device in medical practice is often not realized because the data collected are not systematically characterized, aggregated, and analyzed in a way that can be relied upon to inform regulatory decision-making. By recognizing the value of RWE as an important contributing factor for understanding and regulating medical devices, we hope to encourage the medical community to learn more from routine clinical care than we do today.

² Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393994.pdf>).

³ Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm517504.pdf>)

⁴ Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling ([Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf) <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf>).

⁵ Strengthening Our National System for Medical Device Postmarket Surveillance (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM301924.pdf>).

⁶ Strengthening Our National System for Medical Device Postmarket Surveillance: Update and Next Steps - April 2013 (<http://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf>).

⁷ Strengthening Patient Care: Building a National Postmarket Medical Device Surveillance System (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM435112.pdf>).

⁸ Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge the Clinical Care and Research - August 2015 (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM459368.pdf>).

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FDA will use the criteria described in this guidance to evaluate whether RWD are of sufficient quality to support regulatory decision-making, including potentially generating valid scientific evidence.⁹ FDA relies only upon valid scientific evidence to determine whether there is a reasonable assurance that a device is safe and effective. However, it is possible that RWE can meet this threshold under conditions where the underlying RWD were accurately and reliably captured at clinically relevant time intervals throughout the device lifecycle. Under the right conditions, RWE may be suitable to support the clearance or approval of a new device, or the expansion of the indications for use of devices that are already on the market. RWE may also be used to supplement the total evidence required for such clearances or approvals. Other applications of RWE in premarket decision-making may also be possible, particularly as RWD systems and analysis methodology advance.

Additionally, aggregation of RWD (e.g., in medical device registries) may prove useful as a postmarket control suitable for providing ongoing device safety surveillance and additional evidence for effectiveness. FDA has long applied postmarket controls as a way to reduce premarket data collection, while still ensuring that the statutory standard of reasonable assurance of safety and effectiveness is met.¹⁰ FDA believes that applying postmarket controls to reduce premarket data collection, when appropriate, can help improve patient access to safe and effective medical devices.¹¹

In some cases, a “traditional” clinical trial may be impractical or excessively challenging to conduct. Ethical issues regarding treatment assignment, and other similar challenges, may present themselves when developing and attempting to execute a high quality clinical trial. Analyses of RWD, using appropriate methods, may in some cases provide similar information with comparable or even superior characteristics to information collected and analyzed through a traditional clinical trial. For example, RWD collected using a randomized exposure assignment within a registry can provide a sufficient number of patients for powered subgroup analyses, which could be used to expand the device’s indications for use. However, not all RWD are collected and maintained in a way that provides sufficient reliability. As such, the use of RWE for specific regulatory purposes will be evaluated based on criteria that assess their overall

⁹ “Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.” [21 CFR 860.7(c)(2)]

(<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=860.7>)

¹⁰ The Least Burdensome Provisions of the FDA modernization Act of 1997: Concept and Principles, (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085999.pdf>)

¹¹ Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval, (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393994.pdf>).

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relevance and reliability. If a sponsor is considering using RWE to satisfy a particular FDA regulatory requirement, the sponsor should contact FDA through the pre-submission process.¹²

III. Real-World Evidence

RWE can exist across a wide spectrum, ranging from observational studies within an existing dataset to studies that incorporate planned interventions with or without randomization at the point of care.¹³ Because of the rapidly advancing methodology for generating and interpreting RWD, this guidance will not elaborate on the methodological approaches that can be used. However, when reviewing the use of RWE to support a regulatory decision, FDA will rely on scientifically robust methods and approaches to determine whether submitted RWE is of sufficient quality to support a particular regulatory decision.

Clinical trials are designed to control variability through detailed eligibility criteria and carefully designed clinical protocols performed by specialized research personnel. They require intensive monitoring and data auditing to demonstrate that use of a device produces the expected results. Although useful in establishing a baseline for device performance, clinical trials may be narrow in scope due to practical challenges. In contrast, studies leveraging RWD can potentially provide information on a wider patient population, thus providing information that cannot be obtained through a traditional clinical trial alone. An existing RWD source, however, may have some inherent bias that could limit its value for drawing causal inferences between medical device exposures and outcomes. Therefore, to mitigate potential bias, careful study design is needed, and a study protocol and analysis plan should be created prior to accessing, retrieving, and analyzing RWD, regardless of whether the RWD are already collected (retrospective) or if they are to be collected in the future (prospective design). Protocols and analysis plans for RWD should address the same elements that a traditional clinical trial protocol and statistical analysis plan would cover. FDA recommends use of the pre-submission process when considering the development of a study using RWD in a regulatory submission.

When considering a prospective study design, one should consider whether RWD collection instruments and analysis infrastructure are sufficient to serve as the mechanism for conducting the study, and if they are not, whether it is possible to modify them for such a purpose. Ultimately, if the sources of bias can be mitigated, RWD collected using a prospective study design may be used to generate or contribute to the totality of evidence needed to assess medical device performance.

Because of its nature, the quality of RWE can vary greatly across different data types and sources. Likewise, there are many types of FDA regulatory decisions spanning the Total Product Life Cycle (TPLC) that necessitate different levels of evidence. This guidance does not change

¹² Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>)

¹³ Sherman RE, Steven A, Dal Pan GJ, et al.; Real-World Evidence – What Is It and What Can it Tell Us?; *NEJM*, Dec 2016; 375; 23

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FDA's evidentiary standards for regulatory decision-making, and in each context we will evaluate whether the available RWE is of sufficient quality to address the specific regulatory decision being considered. FDA believes that the increased use of electronic data systems in the healthcare setting has the potential to generate substantial amounts of RWD. Because these systems can vary greatly in terms of quality, not all RWD can by itself generate sufficient evidence to support an FDA regulatory decision. Nevertheless, these RWD may still provide a valuable contribution to the totality of evidence considered for the decision. Furthermore, in order to use RWD, the device must be sufficiently identified with the level of detail necessary to address the regulatory question. For example, to evaluate a particular device, the Unique Device Identifier (UDI) or serial/model number may be necessary to identify the device within a RWD source that contains data on many similar devices.

When RWE is intended to be used for purposes of evaluating a regulatory issue, it is important that the RWD not only follow the criteria described in section V, but are also presented to FDA according to recognized data standards (i.e. in standardized file formats and data structures, utilizing standardized variables and definitions, etc.) when applicable. This includes discussions of the methodology used to analyze RWD and assess clinically relevant differences as well as statistical significance.

IV. Regulatory Context in Which RWE May be Used

A. General considerations for the use of RWE

FDA will consider the use of RWE to support regulatory decision-making for medical devices when it concludes that the RWD used to generate the RWE are of sufficient quality to inform or support a particular regulatory decision. The threshold for sufficient quality will depend on the specific regulatory use of the evidence. For example, a specific registry might be leveraged for postmarket surveillance, but not be adequate to support a premarket determination of reasonable assurance of safety and effectiveness or substantial equivalence.

The collection or aggregation of RWD sources outside of medical records is usually performed for specific pre-determined non-regulatory purposes. For example, medical administrative claims data are typically kept for purposes of billing/payment for medical care. Disease-specific RWD sources sponsored by patient advocacy organizations may be useful for tracking progression or outcomes of specific rare or poorly understood diseases. Treatment-specific RWD sources coordinated by one or more professional societies may have several purposes, including assessment and tracking of overall outcomes, providing data for quality assessment (QA), informing performance improvement (PI) initiatives, or providing risk prediction and benchmarking data for specific therapies. Therefore, the use of RWD for specific regulatory decisions necessitates an understanding of the strengths and limitations of the RWD, and how these qualities impact the relevance and reliability factors described below.

RWD may potentially be used as some or all of the evidence necessary for understanding medical device performance at different points in the TPLC. Some purposes for which RWD may potentially be used include the following:

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- for generating hypotheses to be tested in a prospective clinical study;
- as a historical control, a prior in a Bayesian trial¹⁴, or as one source of data in a hierarchical model or a hybrid data synthesis;
- as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance in a setting where a registry or some other systematic data collection mechanism exists;
- as evidence to identify, demonstrate, or support the clinical validity of a biomarker;
- as evidence to support approval or granting of an Humanitarian Device Exemption, Premarket Approval Application (PMA), or De Novo request;
- as support for a petition for reclassification of a medical device under section 513(e) or (f)(3) of the FD&C Act;
- as evidence for expanding the labeling of a device to include additional indications for use or to update the labeling to include new information on safety and effectiveness^{15,16}
- for public health surveillance efforts. Through ongoing surveillance, signals are at times identified that suggest there may be a safety issue with a medical device. RWE may be used to refine these signals for purposes of informing appropriate corrective actions and communication;^{17,18}
- to conduct post-approval studies that are imposed as a condition of device approval or to potentially preclude the need for postmarket surveillance studies ordered under section 522 of the FD&C Act;

¹⁴ Guidance for Industry and FDA Staff: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, (<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf>)

¹⁵ What We Mean When We Talk About EvGen Part II: Building Out a National System for Evidence Generation, (<http://blogs.fda.gov/fdavoices/index.php/2016/04/what-we-mean-when-we-talk-about-evgen-part-i-laying-the-foundation-for-a-national-system-for-evidence-generation/>)

¹⁶ Guidance for Industry: General/Specific Intended Use (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf>).

¹⁷ Public Notification of Emerging Postmarket Medical Device Signals (“Emerging Signals”) Guidance for Industry and Food and Drug Administration Staff (<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm479248.pdf>).

¹⁸ Strengthening Patient Care: Building an Effective National Medical Device Surveillance System (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM435112.pdf>).

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- in certain circumstances, for use in generating summary reports of Medical Device Reports (MDRs); and
- to provide postmarket data in lieu of some premarket data.

B. Application of Investigational Device Exemption (IDE) Requirements in 21 CFR 812 to the Collection of RWD

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with certain other requirements of the FD&C Act that would apply to devices in commercial distribution. The purpose of this, per 21 CFR 812.1, “is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose.” As explained in Part 812, the IDE regulations apply to all clinical investigations of devices to determine safety and effectiveness, with certain limited exceptions. In many cases, an approved IDE is required before initiating a clinical investigation. An investigation is defined as “a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.”¹⁹

Whether the collection of RWD for a legally-marketed device requires an IDE depends on the particular facts of the situation. Specifically, if the device is being used in the normal course of medical practice, an IDE would likely not be required. Because FDA does not regulate the practice of medicine, this could include administration of a legally marketed device for uncleared or unapproved uses as long as the device is being administered under the authority of a healthcare practitioner within a legitimate practitioner-patient relationship.²⁰ However, if data are being gathered to determine the safety and effectiveness of the device, and the process for gathering the data would influence treatment decisions, such administration would likely not be within the normal course of medical practice, and an IDE may be required. For example, a registry designed to determine the safety and effectiveness of an approved device for a new intended use would likely be subject to IDE requirements if physicians are instructed to treat specific patients or otherwise administer the device in a prescribed way for purposes of data generation, or when certain follow-up activities are performed for the purpose of research. Because the gathering of RWD is different from traditional investigations, we recommend that you contact FDA if you have questions about whether an IDE is required.

As stated above, FDA does not regulate the practice of medicine, and recognizes that RWD may be collected during the routine care of patients that provides information related to the actual use of an approved or cleared device. Such observations may include RWD from a use of a medical device that was not within the cleared or approved indications for use. If such RWD collection

¹⁹ See 21 CFR 812.3(h)

²⁰ FDA will not limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. Section 1006 of the FD&C Act, 21 USC 396.

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does not impact how the device is administered, and the administration is within the normal course of medical care, an IDE would likely not be required. For example, retrospective analyses of existing RWD involving the use of a device that was not within the cleared or approved indications for use would generally not be subject to IDE regulations. In such cases, treatment decisions were made in the best interest of patients according to their clinician's medical judgment at that time. However, if the plan to conduct such analyses impacts patient care, then the study may be subject to IDE requirements.

Should a sponsor or Institutional Review Board (IRB) be unclear regarding the applicability of the IDE regulations to a particular RWD collection activity or use, the sponsor or IRB should contact FDA. If an IDE is determined to be required, FDA will work with the IDE sponsor to develop the least burdensome approach to facilitate the efficient generation of high-quality RWE. Note that regardless of the applicability of 21 CFR 812, FDA regulations at 21 CFR 56 (IRB review), 21 CFR 50 (Informed Consent) and 21 CFR 54 (Financial Disclosure) may apply to RWE generation activities, as may other federal, state, and local laws regarding human subject protections.

V. Characteristics of RWD

FDA does not endorse one type of RWD over another. Sponsors should select appropriate RWD sources based on their suitability to address specific regulatory questions. Whether the RWD resides within paper or electronic medical records, is collected by administrative databases, is abstracted, aggregated and stored in disease- or treatment-specific databases (i.e., registries), or collected and aggregated through other means, accuracy when compared to verifiable source documentation is essential. Verifiable source documentation for RWD elements includes, but is not limited to: paper or electronic inpatient and outpatient medical records and case histories, diagnostic laboratory and imaging data, patient preference information, patient-reported outcome measures, UDI and other device identifiers, and performance data that exist within the device such as self-diagnostics, error codes, and patient diagnoses/treatments delivered. Requirements and needs for individual source data verification will vary with specific regulatory questions, and will contribute to the overall understanding of data quality for that source.

In order to determine the suitability of RWD for regulatory decision-making, FDA will assess the relevance and reliability of the source and its specific elements. This assessment will be used to determine whether the RWD source(s) and the proposed analysis can generate evidence that is sufficiently robust to be used for a given regulatory purpose. Whether evidence is sufficiently relevant and reliable for use will, in part, depend on the level of quality necessary to make a particular regulatory decision. FDA will evaluate the same factors to assess RWD across all data sources and regulatory decisions. In cases where RWE is derived from multiple RWD sources, each RWD source will be evaluated individually and together in the aggregate to determine the relevance and reliability of the RWD. When developing a new RWD source, consultation with FDA and other stakeholders is recommended to ensure that relevance and reliability are addressed in the initial design.

A. Relevance

The relevance of RWD, RWD sources, and resultant analysis is assessed by evaluating several factors as outlined below. These factors can help determine if the data adequately address the applicable regulatory question or requirement, in part or in whole. Questions about the applicability of RWD to a specific case should be discussed with FDA through the pre-submission process.²¹ Relevance of RWD for regulatory decision-making can be assessed prior to a regulatory submission, such as via the pre-submission process, or during the regulatory review process. The overall assessment of relevance should determine whether the existing RWD source is adequate for evaluating the performance of a device in the identified regulatory context (as a sole source or partial source of evidence).

Since RWD sources are usually developed for non-regulatory purposes (e.g., to document care in the case of EHRs or to submit insurance claims for reimbursement in administrative and claims data), FDA will assess whether the individual data elements contained within an existing RWD source are sufficient to be used for a regulatory purpose. The data should be accurate, as complete as possible, and have an appropriate scope to address the question at hand (i.e., data adequacy). The need for review or adjudication of specific outcomes of interest (e.g. stroke or major bleeding) at the patient level may also be assessed. For analysis and interpretation of RWD, it is important to have a pre-defined common set of data elements, a common definitional framework (i.e., data dictionary), and pre-specified time intervals for data element collection and outcome analyses. In assessing the relevance of RWD, FDA will also consider, if warranted, the ability to supplement the available RWD through linkage with other data sources to provide additional or confirmatory data, e.g., with EHR and/or administrative claims data.

Important relevance factors that FDA will assess to determine if the RWD are suitable for regulatory use include, but are not limited to, whether:

- the RWD contain sufficient detail to capture the use of the device, exposures, and the outcomes of interest in the appropriate population (i.e. the data apply to the question at hand);
- the data elements available for analysis are capable of addressing the specified question when valid and appropriate analytical methods are applied (i.e. the data are amenable to sound clinical and statistical analysis); and
- the RWD and RWE they provide are interpretable using informed clinical/scientific judgment. Important considerations for the assessment of this factor include:

²¹ Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff: Guidance for Industry and Food and Drug Administration Staff (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>)

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- whether the use of the device in a real-world population is representative as captured within the data source, and is generalizable to the relevant population being evaluated;
- whether the RWD source is used regionally, nationally and/or internationally;
- the overall percentage of patient exposure to the device that are captured in the RWD source;
- the validation protocols and resultant data that are used to evaluate how well the RWD source reflects the patient population's experience;
- whether the RWD study design, study protocol, and/or analysis plan is appropriate to address the regulatory question and capable of being accomplished in a sufficiently timely manner;
- whether the RWD contains elements to capture specific device identification information (e.g., unique device identifier);
- whether the RWD adequately captures patient medical history and preexisting conditions, as well as follow-up information needed evaluate the question being addressed (e.g., whether administrative claims data have adequate continuity of coverage);
- whether sufficient data elements are collected to adjust for confounding factors that may impact the exposure or outcomes of interest;
- whether any linkages performed are scientifically appropriate and account for differences in coding and reporting across sources;
- the RWD source reporting schedule, including time interval between database close and release, and length of reporting periods;
- the prior documented (e.g., peer reviewed publications or practice guidelines) use of the RWD source for determining outcomes-based quality assessments, validated predictive risk modeling, signal detection, performance improvement, benchmarking, and other clinically-meaningful uses;
- whether the data elements collected are sufficient for assessing outcomes (including adjudication, if necessary); and
- whether supplemental data sources are available and sufficient to provide any missing information or evidence required for an informed decision.

B. Reliability

The reliability of RWD, RWD sources, and resultant analyses is assessed by evaluating several factors as outlined below. The primary factors FDA considers for assessing the reliability of RWD include how the data were collected (data accrual), and whether the people and processes in place during data collection and analysis provide adequate assurance that errors are minimized and that data quality and integrity are sufficient (data assurance). Additionally, the RWD analysis protocol should be prospectively defined as described in section III above. FDA will consider existing data accrual, data assurance, and analysis approaches in its assessment of the fitness of a given RWD source and its data.

(1) Data accrual

To ensure the reliability of RWD, the RWD source should have an operational manual or other documentation that pre-specifies the data elements to be collected, data element definitions (i.e., data dictionary to provide a common definitional framework), methods for data aggregation and documentation (e.g., common case report form, abstraction from verifiable sources), and the relevant time windows for data element collection (i.e., common temporal framework). Some RWD sources such as EHRs or claims data may not fulfill all of these characteristics, but may still demonstrate sufficient reliability to support regulatory decision-making. Factors FDA will consider in making this determination include (but are not limited to):

- the preparedness of individual sites for complete and accurate collection of RWD (e.g., whether there are defined processes, site training and support, and qualified personnel);
- whether a common data capture form was used;
- whether a common definitional framework (i.e., data dictionary) was used;
- adherence to a common temporal framework for collection of key data points;
- the timing of establishing the study plan, protocol, and/or analysis plan relative to collection or retrieval of the RWD;
- the sources and technical methods used for data element capture (e.g., chart abstraction, point of care entry, EHR integration, UDI capture, data records from the device, and linkage to claims data);
- whether patient selection and enrollment criteria minimize bias and ensure a representative real-world population (e.g., all-comer's design, consecutive patient enrollment);
- the timeliness of data entry, transmission, and availability; and

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- whether necessary and adequate patient protections were in place (e.g., methods to protect patient privacy, and need for informed consent as determined by the reviewing IRB and in compliance with FDA regulations).

(2) Data assurance - Quality Control

Data quality control is essential for providing confidence in the reliability of RWD and RWE sources. RWD quality can generally be improved by following published recommendations concerning registries, such as those by the Agency for Health Care Quality, Patient-Centered Outcomes Research Institute,²² the National Medical Device Registry Task Force,²³ and the Regulators Forum (IMDRF) Registry Working Group.²⁴ However, certain sources of RWD, such as some administrative and healthcare claims databases or EHRs, may not have established data quality control processes and may not be capable of fully implementing or following the above recommendations. When considering a source of RWD for regulatory purposes, it is important to consider any methods and systems used to help ensure sufficient data quality. Potential RWD sources should be evaluated in accordance with the data QA plan and procedures developed for the data source itself. Since evaluation of RWD sources may not always permit specific line item source verification, important factors for consideration include:

- the quality of data element population (e.g., whether abstracted from a verifiable source to assess transcription errors or automatically populated through a data extraction algorithm);
- adherence to source verification procedures and data collection and recording procedures for completeness and consistency;
- completeness (i.e., minimized missing or out of range values) of data necessary for specified analyses, including adjustment for confounding factors;
- data consistency across sites and over time;²⁵

²² AHRQ Registries for Evaluating Patient Outcomes: A User's Guide 3rd Edition, Volume 1 Chapter 11, Data Collection and Quality Assurance and Volume 2 Chapter 25, Assessing Quality.

(<http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&mp=1&productID=1897>)

²³ A Report from the Medical Device Registry Task Force & the Medical Devices Epidemiology Network. Recommendations for a National Medical Device Evaluation System. Strategically Coordinated Registry Networks to Bridge Clinical Care and Research, August 2015. Available at:

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm459368.pdf>. Accessed August 6, 2016.

²⁴ IMDRF Registry Essential Principles. Available at:

<http://www.imdrf.org/docs/imdrf/final/consultations/imdrf-cons-essential-principles-151124.pdf>. Accessed August 3, 2016

²⁵ PCORI Conduct of Registry Studies

<http://www.pcori.org/sites/default/files/Standards-in-the-Conduct-of-Registry-Studies-for-Patient-Centered-Outcomes-Research1.pdf>

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- evaluation of on-going training programs for data collection and use of data dictionaries at participating sites;
- evaluation of site and data monitoring practices; and
- the use of data quality audit programs.

The use of routine medical care data for additional analyses often relies on data cleaning and cross-referencing. These techniques can confirm the data's internal consistency and identify missing values, but cannot fully determine data accuracy and authenticity. In traditional clinical research, an audit that compares source documents to entered data is often an essential step to verify the accuracy and completeness of the data. Study monitoring through various methods, such as remote monitoring, also plays an important role.²⁶ These types of data verification activities are equally important for RWD that is intended to be used for regulatory purposes.

Regardless of the original purpose for collecting the RWD, procedures for data collection and quality assurance should be put into place during the data source design and development stages (when applicable) to optimize the reliability, quality and usefulness of the data. The data collection procedures used for data platforms such as registries should be clearly defined and described in a detailed data management standard operating procedures (SOP) manual. When implementing a retrospective study using RWD, standardizing procedures to ensure the use of uniform and systematic methods for collecting and cleaning data are vital to ensuring data quality. For example, a "quality system approach" with a risk-based quality assurance and monitoring plan is a practical strategy for data platforms such as registries that can be challenging to audit. The RWD source organization or entity considering using the RWD for regulatory purposes should retain records regarding the assessment of adherence to the RWD source's established data quality assurance and quality control policies and procedures.

VI. Examples Where RWE is Used

The following examples are generalized from actual uses of RWE in support of regulatory decision making. These examples do not represent a comprehensive list of all potential uses or sources of RWD, but do describe some situations where RWE might be used to support regulatory decision-making.

A. Expanded Indications for Use

The National Cardiovascular Data Registry (NCDR) was created in 1997 by the American College of Cardiology (ACC) as "an exploration into strategies for improving cardiovascular care through the use and application of clinical data." These registries are designed to help participants measure, benchmark, and improve cardiovascular care. In particular, the Registry for diagnostic cardiac CATHeterization and Percutaneous Coronary Intervention (Cath-PCI

²⁶ Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (PCORI Conduct of Registry Studies (<http://www.pcori.org/sites/default/files/Standards-in-the-Conduct-of-Registry-Studies-for-Patient-Centered-Outcomes-Research1.pdf>))

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Registry) “assesses the characteristics, treatments and outcomes of cardiac disease patients who receive diagnostic catheterization and/or percutaneous coronary intervention (PCI) procedures, measuring adherence to ACC/AHA clinical practice guideline recommendations, procedure performance standards and appropriate use criteria for coronary revascularization.” As a registry collecting RWD on patients treated in routine clinical practice with an approved or cleared device, an IDE is not required even though a substantial volume of RWD is generated for uses outside of the device’s cleared or approved indications for use. RWD from this registry could be used to identify opportunities to expand the labeling of devices captured in the registry. Should a manufacturer wish to expand indications, this type of RWD might provide sufficient evidentiary support, depending on the specific devices, indications, and analyses.

Another example is a Class III device that, due to technological advances in its design, has seen an expansion of clinically acceptable use that is outside of the device’s approved indications for use. There is little published data to support a reasonable assurance of safety and effectiveness of the new use. To address the lack of data to support new indications for use, relevant medical societies have established a national registry to collect safety and effectiveness information for all patients implanted with this specific device at participating institutions. This registry also uses a validated matching algorithm to link registry records with administrative healthcare claims as a supplemental dataset for capturing long-term outcomes. A study using the registry data collection and analysis infrastructure was initiated with an approved IDE application since the study focused on a use of this device that was not within the approved indications for use and imposed changes to the collection regiment of specific follow-up data that might not otherwise have occurred as part of routine medical care. FDA is hopeful that the RWD may be of sufficient quality to address critical safety questions and to potentially support labeling changes or other regulatory decisions for this device.

B. Postmarket Surveillance Studies (Section 522)

FDA has issued a series of postmarket surveillance orders, related to investigating patient safety issues for a type of class II device, under the authority of section 522 of the FD&C Act. These 522 orders covered multiple devices from different manufacturers that are similar in intended use, design, and other characteristics, such that the surveillance questions were identical. To comply with the orders, many manufacturers decided to collaborate with a clinical professional society in this field and with FDA to develop a patient registry that would collect the needed data to address the public health questions. An IDE was not required because the 522 order was focused on device uses consistent with the labeling. The resultant registry was designed to collect RWD on all patients with the relevant condition, including those treated with the devices of interest, with other devices, and through medical management. Manufacturers are able to share the comparator group consisting of treatments that do not use the devices of interest. In addition, because the registry was designed at the outset to produce regulatory-quality RWD in addition to meeting research and quality improvement purposes, appropriate data quality checks and electronic controls were a part of the initial design and implementation. Since this registry development process took a substantial amount of time, FDA was willing to grant extensions to manufacturers to respond to the 522 orders as long as progress was being made. The registry was also designed to allow for its use (with additional protocols and other traditional study

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operational elements) in conducting premarket studies that could support future premarket submissions.

C. Post-Approval Device Surveillance as Condition of Approval

Permanent implants are typically designed to serve patients for a time period that is much longer than what can reasonably be captured in a premarket clinical trial. For example, a trial that follows patients for two years after implantation would not produce data for the designed life span of 7 to 10 years for that implanted device. Traditionally, FDA would require extended follow-up of the premarket patient cohort and an additional new-enrollment study designed to capture hundreds to thousands of patients with follow-up for the life of the implanted device. Some clinical professional societies have developed registries that collect RWD on patients receiving these devices. FDA has worked with manufacturers and professional societies to evaluate the registries and has found that they can be reliable for certain health outcomes of interest. Should sufficient RWD exist that are capable of addressing the questions for which a Post-Approval Study (PAS) requirement may be issued, FDA may instead issue a condition of approval that requires collection/reporting of these RWD on the device.

For example, a new breakthrough Class III medical device was approved based on prospective, randomized, and controlled clinical trial data. Early in the PMA review process, the manufacturer began to consider postmarket commitments, and began discussions with FDA and other stakeholders. A registry was launched that generated RWD that could meet FDA's data requirements, as well as others. Because the new registry was constructed early enough to collect information about all patients receiving this device upon approval, FDA could provide an earlier device approval conditioned on further robust RWD collection and reporting in the postmarket setting. This registry has since been used to a) collect surveillance data on subsequent devices with similar designs and indications, b) collect and retrospectively analyze RWD on all uses of the devices to support new expanded indications for use, and c) support embedded prospective clinical investigations under IDE for new devices and new generations of approved devices. No IDE is necessary for the general data collection activities of the registry, as it collects RWD on all uses of otherwise approved medical devices and it does not influence the treatment decisions and/or follow-up care that patients receive. The retrospective analysis of RWD for uses that are outside the approved indications for use did not require an IDE because treatment decisions were not influenced by the expectation of conducting the future analysis, but was still reviewed by an IRB for human subject protection issues. However, prospective enrollment in a clinical investigation using the registry infrastructure to study a new, unapproved significant risk device would require an IDE. Similarly, a prospective, non-observational clinical investigation of a new indication for an approved device may require an IDE, depending on the risk determination.

D. Control Group

A manufacturer approached FDA during the development of a next generation medical device that had substantial technological changes from previous iterations of that specific device and other similar devices from other manufacturers. FDA determined that clinical evidence was needed to support an approval decision for this device modification. A registry exists that captures RWD on all uses of medical devices with a similar intended use. The manufacturer

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designed a clinical study that compared the use of the new device to a non-randomized concurrent control group derived from the registry. The existing registry was evaluated by FDA and the manufacturer according to the factors cited in this guidance and was found to provide sufficiently relevant and reliable RWD on the control population, such that the manufacturer did not have to collect additional data from these patients or influence the course of their clinical care in any way. The patients who received the investigational device were enrolled under an approved IDE. However, the patients who contributed to the control group were not considered part of the IDE because they were enrolled in a national registry that collected RWD on FDA approved devices, and their treatment was not influenced by the existence of the study.

E. Supplementary Data

Periodically, FDA identifies an issue related to the safety of a marketed medical device that was not detected in premarket trials. In the case where RWD has been systematically collected, FDA has used these RWD, in combination with case reports, publications, adverse event reports, engineering and nonclinical test data, and other sources of information available to FDA to gain a better understanding of the severity of the issue, precipitating factors, affected populations, and alternative therapies. The addition of RWD has proven extremely valuable as a means to develop a course of action that best protects public health in these instances.

For example, a class III device was under review for a new indication. The manufacturer provided data from a prospective clinical trial with limited follow-up information and inadequate data from the control group, which made interpretation of results difficult. However, a pre-existing registry was already collecting and reporting RWD on the control therapies. The registry data were used to supplement and help interpret the clinical trial data, allowing FDA to come to an appropriate regulatory decision without requiring additional clinical trial data. Without the RWE, additional study subjects could have been exposed to a device with a questionable risk-benefit balance. Coming to a final decision more quickly in this case protected subjects' health while also spurring development of new designs for the medical device.

F. Objective Performance Criteria and Performance Goals

An Objective Performance Criterion (OPC) refers to a numerical target value derived from historical data from clinical studies and/or registries and may be used in a dichotomous (pass/fail) manner for the review and comparison of safety or effectiveness endpoints.²⁷ An OPC is usually developed when device technology has sufficiently matured and can be based on publicly available information or on information pooled from all available studies on a particular kind of device. Similar to OPC, a performance goal (PG) refers to a numerical value that is considered sufficient for use in the evaluation of an investigational device regarding a safety and/or effectiveness endpoint. But, generally, the device technology is not as well-developed or

²⁷ Design Considerations for Pivotal Clinical Investigations for Medical Devices - Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff for more information on OPCs and PGs. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf>.

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mature for use of a PG as for an OPC, and the data used to generate a PG are not considered as robust as those used to develop an OPC. A PG might be considered for patient populations that are difficult to study or if there is no clinical equipoise for any control. From a sufficiently relevant and reliable RWD source, a PG can be constructed using appropriate statistical methods, such as a subject-level meta-analysis. As technology evolves over time, an OPC or PG could be updated using RWD.

VII. Glossary

The following definitions are supplied to provide the reader with an understanding of the specific terms used in this guidance. These definitions should not be construed to be new interpretations or clarification of the use of similar words or phrases in the FD&C Act, related code or regulation, other federal, state, or local laws, or other guidance documents.

- **Bias**—“Bias is any systematic error in the design, conduct, analysis, interpretation, publication, or review of a study and its data that results in a mistaken estimate of a treatment’s effect on disease. This systematic error results from flaws in the method of selecting study participants, in the procedures for gathering data, and in the decision of how and whether to publish the results. These flaws can lead to observed study results that tend to be different from the “true” results. Bias can be minimized by ensuring that the study design is appropriate for addressing the study hypotheses and establishing and carefully monitoring procedures of data collection that are valid and reliable.”²⁸
- **Confounding**—“A situation in which a non-causal association between a given exposure or treatment and an outcome is observed as a result of the influence of a third variable designated as a confounder. The confounding variable needs to be related to both the treatment and the outcome under study. Confounding is distinct from bias because this association, while not causal, is real.”²⁹
- **Electronic Health Record (EHR)**—“An electronic record of health-related information on an individual that conforms to nationally recognized/utilized interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization.”³⁰
- **Electronic Medical Record (EMR)**—“An electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one health care organization.”³¹

²⁸ JM Last. A dictionary of Epidemiology (3rd edition). New York: Oxford University Press, 1995) (M Szklo & FJ Nieto. Epidemiology: Beyond the basics. Gaithersburg, MD: Aspen Publishers, Inc., 2000

²⁹ L Gordis. Epidemiology. Philadelphia: WB Saunders, Co., 1996

³⁰ The National Alliance for Health Information Technology Report to the Office of the National Coordinator for Health Information Technology on Defining Key Health Information Technology Terms April 28, 2008. (<http://www.himss.org/national-alliance-health-information-technology-report-office-national-coordinator-health>).

³¹ The National Alliance for Health Information Technology Report to the Office of the National Coordinator for Health Information Technology on Defining Key Health Information Technology Terms April 28, 2008. (<http://www.himss.org/national-alliance-health-information-technology-report-office-national-coordinator-health>)

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- **Interventional Study**—“A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.”³²
- **Large Simple Trial** – “A large simple trial (LST) is a type of randomized clinical trial (RCT) ideally suited to answer many important clinical questions and because it typically answers only one or two questions in a broader patient population, is generally more efficient and less expensive than other large RCTs. LSTs have a large sample size and statistical power to detect clinically relevant treatment effects, providing unambiguous results and minimizing the effects of random errors.”³³
- **Medical Administrative Claims Data**—“Claims data arise from a person’s use of the health care system [and reimbursement of health care providers for that care].”³⁴
- **Medical Device Registry** – “Organized system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system) with a primary aim to improve the quality of patient care.”³⁵
- **Medically Recognized Standards of Care**—“Medically recognized standards of care are treatments or procedures that have been accepted by medical experts as appropriate treatments or procedures for a given type of disease or condition and are commonly used by health care professionals. The medical recognition of standards of care is typically represented by publication in a peer-reviewed journal or some form of recognition by a professional medical society. The evidentiary bases for these recognized standards of care vary.”³⁶
- **Observational Study**— “A study that does not involve any intervention (experimental or otherwise) on the part of the investigator; e.g., a population study in which changes in health status are studied in relation to changes in other characteristics. Most analytical epidemiological designs (notably, case-control and cohort studies) are properly called observational because investigators observe without intervening other than to record, classify, count, and analyze results.”³⁷

³² <https://www.clinicaltrials.gov/ct2/about-studies/glossary>

³³ Project: Large Simple Trials; Clinical Trials Transformation Initiative (<https://www.ctti-clinicaltrials.org/projects/large-simple-trials>)

³⁴ Strom, Brian. *Pharmacoepidemiology*. Chichester, England: John Wiley and Sons, 2005.

³⁵ IMDRF Registry Essential Principles. Available at: <http://www.imdrf.org/docs/imdrf/final/consultations/imdrf-cons-essential-principles-151124.pdf>. Accessed August 3, 2016

³⁶ Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions: Workshop in Brief 2015, Institute of Medicine (<https://www.nap.edu/read/21668/chapter/1>)

³⁷ A Dictionary of Epidemiology (6 ed.) Oxford Reference <http://irea.ir/files/site1/pages/dictionary.pdf>

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- **Postmarket surveillance**— “Postmarket surveillance is the active, systematic, scientifically valid collection, analysis and interpretation of data or other information about a marketed device.”³⁸
- **Pragmatic clinical trial (PCT)** - A clinical trial “designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.”³⁹
- **Prospective Study**—“A prospective study design (also called a *concurrent cohort study*) defines the original population of interest at the start of the study and collects exposure/treatment and outcome data from that time point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated.”⁴⁰
- **Real-World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- **Real-World Evidence (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.
- **Registry**—“An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical or policy purposes.”⁴¹
- **Retrospective Study**—“A retrospective study design (also called a *retrospective cohort study, a historical cohort, or non-concurrent prospective study*) defines the population and determines the exposure/treatment from historical data (i.e., data generated prior to the initiation of the study). The variables and outcomes of interest are determined at the time the study is initiated. Some studies are a combination of concurrent and retrospective cohort designs where the exposure/treatment is ascertained from existing objective records (e.g., medical records, claims data), and follow up and measurement of the outcome continues into the future.”⁴²

³⁸ 21 CFR 822.3

³⁹ Adapted from Califf R and Sugarman J; Exploring the Ethical and Regulatory Issues in Pragmatic Clinical Trials; *Clin Trials*, 2015 Oct;12(5):436-41. doi: 10.1177/1740774515598334. Epub 2015 Sep 15

⁴⁰ JM Last. A dictionary of Epidemiology (3rd edition). New York: Oxford University Press, 1995) (M Szklo & FJ Nieto. Epidemiology: Beyond the basics. Gaithersburg, MD: Aspen Publishers, Inc., 2000

⁴¹ Registries for Evaluating Patient Outcomes: A User's Guide (<https://www.effectivehealthcare.ahrq.gov/ehc/products/420/1897/registries-guide-3rd-edition-vol-1-140430.pdf>)

⁴² JM Last. A dictionary of Epidemiology (3rd edition). New York: Oxford University Press, 1995) (M Szklo & FJ Nieto. Epidemiology: Beyond the basics. Gaithersburg, MD: Aspen Publishers, Inc., 2000

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- **Surveillance**—“Surveillance is a continuous and systematic process of collection, analysis, interpretation, and dissemination of descriptive information for monitoring health problems.”⁴³
- **Traditional clinical trial**—Traditional clinical trials are typically conducted in specialized research settings with specific populations. They often utilize measures designed to control variability and ensure data quality, such as detailed eligibility criteria, detailed case report forms that exist apart from ordinary medical records, and intensive monitoring and auditing designed to ensure precise adherence to study procedures and rigorous precision in data collection. They typically also include substantial efforts to ensure compliance with treatments and to avoid concomitant treatments that might influence the randomized treatment effect.

⁴³ JW Buehler. Surveillance (Ch. 22) pages 435-458 in KJ Rothman & S Greenland (editors) Modern Epidemiology 2nd edition. Philadelphia: Lippincott-Raven Publishers, 1998