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

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Document issued on July 27, 2016.

This guidance was updated September 16, 2016 to correct a missing footnote.

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Food and Drug Administration
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Preface

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

FDA is issuing this draft guidance to clarify how we evaluate real-world data to determine whether it may be sufficiently relevant and reliable to generate the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices.

- **Real-World Data (RWD)** is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.

- **Real-World Evidence (RWE)** is the evidence derived from aggregation and analysis of RWD elements.

RWD and associated RWE could constitute valid scientific evidence, depending on the characteristics of the data. This guidance should not be interpreted to convey that FDA is changing the evidentiary standards used in regulatory decision-making; rather, this guidance

describes the circumstances under which RWD may be used in different FDA contexts based on the existing evidentiary standards.

This guidance 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. However, this guidance does not address the use of non-clinical data, adverse event reports, and secondary use of clinical trial data (e.g., post hoc analyses). In addition, this document does not provide guidance about good study design methods, conduct, or statistical methodology.

This guidance does not affect any federal, state or local laws or regulations or foreign laws or regulations that may otherwise be applicable to the use or collection of real-world evidence and that provide protections for human subjects or patient privacy. When finalized, 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 draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency 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 data 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 controls for data quality and against biased results as data collected within a clinical trial setting. However, under certain 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 electronic health records (EHRs), registries, and administrative and claims data, may provide new insights into the performance of medical devices. The information obtained could potentially be used to aid FDA in regulatory decision-making.

FDA has issued guidance on balancing premarket and postmarket data collection,[2] understanding benefit-risk determinations,[3] and expedited access to medical devices for unmet medical needs[4]

[1] FDA's What We Do
[2] Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval

in an attempt to streamline the process for bringing new technologies to market while assuring robust evidence generation and applying appropriate controls to ensure the continued safety and effectiveness of medical devices. FDA has also issued plans for and has begun implementation of a national evaluation system[5,6,7,8] that leverages RWD to more quickly identify safety problems, to better understand the benefit-risk profile of devices used in clinical care, and to reduce the time and cost of evidence generation to inform FDA premarket approval and clearance.

Routine clinical practice often involves the use of cleared or approved devices for uses or in patient populations not within the cleared or approved indications for use. However, the advances in knowledge that may result are often not realized because the data collected are not systematically characterized, aggregated, and analyzed in a way such that it 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 medical device researchers, manufacturers, physicians, hospitals and other stakeholders to learn more from routine clinical care than we do today.

FDA will use the criteria described in this guidance to help determine if RWD data sources are of sufficient quality to potentially generate 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. While it is required that this bar be met in all such cases, it is possible that RWD could meet this threshold under circumstances when important and necessary patient data were accurately and reliably captured at clinically relevant time intervals throughout the appropriate portions of the lifecycle of the medical device. For example, RWE may be suitable to support the expansion of the indications for use of cleared or approved devices through an appropriate premarket submission. RWE may also be suitable to augment the information needed to support clearance or approval of the next generation of a device. Other applications of RWE in premarket decision-making may be possible, as well, particularly as data systems and analysis methodology advance. Aggregation of RWD (e.g., in medical device registries) may

[3] Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

[4] Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

[5] Strengthening Our National System for Medical Device Postmarket Surveillance

[6] Strengthening Our National System for Medical Device Postmarket Surveillance: Update and Next Steps - April 2013

[7] Strengthening Patient Care: Building a National Postmarket Medical Device Surveillance System

[8] Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge the Clinical Care and Research - August 2015

[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)]

also prove useful as a postmarket control suitable for providing ongoing information for device safety surveillance and for providing additional evidence for effectiveness. FDA has long applied postmarket controls as a way to reduce premarket data collection where appropriate, while assuring that the statutory standard of reasonable assurance of safety and effectiveness is still 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 challenging to conduct, given the realities of medical device innovation and development cycles, ethical issues that may arise with treatment assignment, and other similar challenges in executing traditional trials with high quality. Analyses of RWD, using appropriate methods, may in some cases provide similar information with comparable or even superior characteristics to information collected through a traditional clinical trial. However, since not all RWD are necessarily collected and maintained in a way that provides sufficient reliability, the use of RWE for specific regulatory purposes will be considered based on criteria that assess the RWD's overall relevance and reliability, including the level of quality necessary for that type of regulatory action or decision. If a sponsor is considering the use of RWE to meet data requirements to support a regulatory decision by FDA, the sponsor should contact FDA through the pre-submission process.[12]

III. Real-World Evidence

RWE has the potential to contribute to a fuller understanding of the benefits and risks to patients when using a medical device. However, it must also be understood that RWE, as with other types of evidence, may be limited due to the underlying relevance and reliability of available data sources, which can impact the value of the gathered information. For example, because some RWD collections are designed for purposes of documenting delivery of care (e.g., EHR, administrative and claims data, quality improvement registries), they may not contain sufficient information to identify or evaluate the performance of a specific medical device. Furthermore, differences in data entry practices from institution to institution may lead to inconsistent data quality that can affect whether certain data is appropriate for regulatory use. Nevertheless, in some cases these data sources may be of sufficient quality and reliability to provide evidence that can be used to support regulatory decision-making.

Prospective clinical trials are designed to limit sources of bias and confounding factors, so that the association between the exposure (treatment) and outcomes can be assessed. In addition, well-controlled clinical trials provide a framework for inferring causal relationships. Similarly, collection and analysis of RWD should be performed in such a manner as to limit bias and assess the association between the exposure and outcome of interest. In some circumstances, RWD can provide information on real-world device use and performance from a wider patient population

10 The Least Burdensome Provisions of the FDA modernization Act of 1997: Concept and Principles
11 Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval
12 Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

than a more traditional clinical trial, and thus provide information that cannot be obtained through a traditional clinical trial alone. However, retrospective analysis of RWD may have some inherent bias that could limit its value as RWE (e.g., the inability to draw causal inferences between medical device exposure and outcome). Therefore, at a minimum, a prospective analysis plan is needed and, in some circumstances, a prospective trial or a traditional clinical trial may be necessary to generate sufficient evidence for a regulatory decision. When considering a prospective trial, one should consider whether RWD collection instruments (e.g., registries) and analysis infrastructure are sufficient to serve as the mechanism for conducting the trial, and if they are not, whether it is possible to modify them for such a purpose. Ultimately, RWD collected using a prospective trial design may be used to generate or contribute to the totality of evidence needed to assess medical device performance if the sources of bias can be sufficiently mitigated. In many cases, this will require that the RWD sufficiently capture detailed device identifiers and other relevant variables to facilitate the analysis of specific devices and clinical contexts of use in a systematic manner.

Because of its nature, the quality (i.e., relevance and reliability) of RWD can vary greatly across sources. Likewise, there are many types of FDA regulatory decisions with varying levels of evidentiary needs. FDA's evidentiary standards for regulatory decision-making are not changing, and in each context we will evaluate whether the available RWD is of sufficient relevance and reliability 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. However, because these systems can vary greatly in terms of quality, not all generated data will be sufficient evidence to support an FDA regulatory decision. Even so, these RWD may still provide a valuable contribution to the totality of evidence considered for the decision.

When RWE is intended to be used for purposes of evaluating a regulatory issue, it is important that the data not only follows the criteria described in section V, but is also presented in a standardized file format and data structure, and adhere to a recognized common data model, if applicable, as data would be presented from clinical trials. This includes discussions of the analytical methodology used to perform calculations related to statistically significant and clinically relevant differences between groups.

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 clinical data contained within RWD source(s) used to generate the RWE are of sufficient quality to provide confidence in the analyses necessary to inform or support the regulatory decision throughout the total product life cycle. The threshold for sufficient quality will depend on the specific regulatory use of the evidence. For example, a specific patient registry might be informative for postmarket surveillance, but not adequate for a premarket determination of safety and effectiveness, while another patient registry may be suitable to address both pre- and postmarket evidence requirements.

The collection or aggregation of RWD sources outside of the medical record is usually performed for specific pre-determined non-regulatory purposes, which may or may not be directly related to individual clinical care. For example, medical administrative claims data sources are typically populated to provide the information needed for 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 primary purposes including assessment and tracking overall outcomes, providing data for quality assessment (QA), informing performance improvement (PI) initiatives, or allowing risk prediction and benchmarking for specific procedural or device therapies applied during one or more episodes of care for various specified conditions.

RWE may potentially be used in many ways to understand medical device performance at different points in the total product life cycle, including but not limited to:

- generation of hypotheses to be tested in a prospective clinical study;
- as a historical control, a prior in a Bayesian trial, or as one source of data in a hierarchical model or a hybrid data synthesis;
- in a setting where a registry or some other systematic data collection mechanism exists, RWD can potentially be used as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance;
- in some circumstances where real-world use of a device is in a broader patient population or wider set of circumstances than described in the device labeling, it may be possible to use existing systematically collected RWD to expand the labeling to include additional indications for use or to update the labeling to include the new information on safety and effectiveness;
- for public health surveillance efforts. Under a surveillance paradigm, RWD is used to understand the evolution of the benefits and risks of medical devices after they have been approved or cleared in the United States. In some cases, ongoing surveillance will result in the identification of a signal that suggests there is an issue with a medical device. RWE may be used to refine these signals to inform appropriate corrective actions and communication;[13]
- to conduct post-approval studies that are imposed at the time of device approval or postmarket surveillance studies ordered under Section 522 of the FD&C Act. Traditionally, these studies have required developing and maintaining traditional clinical trial enterprises; however, as RWD methodology and infrastructure grow, RWE may be

[13] Strengthening Patient Care: Building an Effective National Medical Device Surveillance System

well-suited to address the issues identified by FDA; the availability of RWE would not lead to more required studies but could reduce the time and cost of evidence generation to meet postmarket requirements;

- RWE can, in certain circumstances, be used in lieu of submitting individual Medical Device Reports (MDRs); and

- to provide postmarket data in lieu of some premarket data under the Expedited Access Pathway (EAP) program. This may be facilitated through the building of an appropriate RWE generation and analysis system.[14]

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 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, and, 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.[15]"

Whether the collection of RWD could be subject to the IDE regulations depends in part on whether that collection constitutes a clinical investigation. Several factors can inform this determination, including the purpose for which the data is being gathered, whether the process for gathering the data would influence treatment decisions, and whether the rights, safety and welfare of human subjects are impacted, among other things. The collection of RWD that is initiated for the specific purpose of determining the safety and effectiveness of a device may be considered a clinical investigation as described above. For example, a registry designed to determine the safety and effectiveness of an approved device for a population solely outside the approved indication could be considered an investigation that could be subject to IDE regulations. Because the gathering of RWD is unique from traditional investigations, we believe that the determination of whether an IDE is required should be made on a case-by-case basis, and we recommend that you contact FDA about whether an IDE is required in cases where RWD collection is initiated for purposes of determining the safety and effectiveness of a device.

[14] Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

[15] See 21 CFR 812.3(h)

However, FDA does not regulate the practice of medicine,[16] and recognizes that some RWD is collected for purposes other than establishing the premarket safety and effectiveness of a device, such as the collection of information related to the actual use by clinicians of an approved or cleared device and/or treatment approaches for a particular disease or condition. Such observations may include RWD from a use of a medical device that was not within the cleared or approved indications for use. When such RWD collection is not intended to determine the safety and effectiveness of the device for purposes of supporting a marketing application to FDA, it would likely not meet the definition of a clinical investigation, and the IDE regulations would not necessarily apply. However, even if an approved IDE is not required for a certain data collection, depending on the factors described below, such data could still meet all the criteria to support use in FDA regulatory decision-making.[17]

Should a sponsor or Institutional Review Boards (IRB) be unclear regarding the applicability of the IDE regulations and need for submission and approval of an IDE for a given data collection activity, the sponsor or IRB should contact FDA. If an IDE is determined to be required for RWE generation activities, FDA will work with the IDE sponsor on the least burdensome approach to facilitate the efficient collection of high-quality data. Note that regardless of FDA's position related to the applicability of 21 CFR 812, FDA regulations at 21 CFR 56 (IRB review) and 21 CFR 50 (Informed Consent) may apply for RWE generation, 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. RWD sources should be selected based on the ability to address specific regulatory questions. Collection of RWD should not dictate, interfere with or alter the normal clinical care of the patient, including choice of treatment. 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 observational databases (i.e., registries), or collected and aggregated through other means, accuracy when compared to verifiable source documentation is essential. Verifiable source documentation, which is the origin of 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-reported outcome measures, and medical device performance data that exists within the device such as self-diagnostics, error codes and patient diagnoses/treatments delivered (including unique device identifier (UDI)).

Important factors regarding RWD that FDA will assess include the relevance and reliability of the source and its specific elements. The underlying data should be robust (i.e., provide

[16] This means that 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.

[17] Any documentation created for the purpose of treating the individual patient and that is also used for regulatory decision-making remains subject to applicable laws and regulations concerning patient privacy and human subject protection.

meaningful information under a variety of conditions) for the purposes and analyses for which it was designed. These assessments will be used to determine whether the data source(s) and the proposed analysis generate evidence that is sufficiently robust to be used for a given regulatory purpose. That is, the threshold for whether RWD is sufficiently relevant and reliable for use will depend on the level of quality required and/or necessary to make a particular regulatory decision. These factors for assessing the value of RWD sources apply to all FDA regulatory uses of the data.

In cases where RWE is derived from multiple data sources, each data source will be evaluated individually and together in the aggregate to determine the relevance and reliability of the RWD to address the specific regulatory question. Assessments of RWD will be applied similarly to existing sources and to new collections of 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

Regulatory relevance of RWD and the data source means that the data adequately addresses the applicable regulatory question or requirement, in part or in whole. FDA will assess the relevance of RWD and RWD sources as a part of the evaluation of the regulatory issue being addressed. Questions about the applicability of RWD to a specific case should be addressed to FDA through the pre-submission process[18]. Relevance of RWD for regulatory decision-making can be assessed either prior to a regulatory submission such as via the pre-submission process, or during the regulatory review process.

Since data elements for existing RWD sources are determined in advance and are primarily chosen for non-regulatory purposes (e.g., quality assurance (QA) and quality improvement (QI) in the case of clinical care registries), FDA will assess whether the individual data elements contained within the existing RWD source are sufficient (i.e., complete, well-defined, and appropriate in scope and timing) to fulfill a regulatory purpose. The overall assessment must conclude that the existing observational data source is reliable, complete, consistent, accurate, and contains all critical data elements necessary for evaluating the performance of a device in the applied regulatory context, including as a part of a larger set of evidence. The need for review or adjudication of specific outcomes of interest may also be assessed if this information is not provided. For collection and interpretation of RWD, it is critical 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 order to ensure the uniformity of data collection and its interpretation. The ability to reliably supplement the available data through linkage with other data sources (e.g., EHR and administrative claims data) to provide additional or confirmatory data will also be considered when assessing relevance of the RWD.

[18] 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

Important factors related to relevance that FDA will assess to determine if the RWD is suitable for use in regulatory decision-making include:

a. the representativeness of the device use in a real-world population as captured within the data source and the generalizability of the data to the relevant population being evaluated;

b. the use and recognition of the RWD source regionally, nationally and/or internationally, and the overall percentage of patient care encounters with the device that are captured;

c. validation protocol and resultant data to evaluate how well the RWD source reflects the patient population's experience;

d. whether the RWD contains elements to capture specific device identification information (e.g., unique device identifier);

e. whether the data adequately captures the duration and extent of patient care necessary to assess patient medical history and preexisting conditions, and follow-up sufficient to evaluate the question being addressed (e.g., whether administrative claims data has adequate continuity of coverage);

f. whether the data contains sufficient detail to capture the use of the device, exposures, and the outcomes of interest in the appropriate population;

g. whether the data elements available for analysis will be capable of addressing the specified question when valid and appropriate analytical methods are applied;

h. whether any linkages performed are scientifically appropriate and undertaken to account for differences in coding and reporting across sources;

i. data source reporting schedule, including time interval between database close and release, and length of reporting periods; and

j. the prior documented (e.g., peer reviewed publications or practice guidelines) use of the data source for determining outcomes-based quality assessments, validated predictive risk modeling, signal detection, performance improvement, benchmarking, and other clinically-meaningful uses.

B. Reliability

FDA will assess the reliability of the data and the data sources by evaluating several factors as outlined below. Primary factors FDA considers for assessing the reliability of RWD include how the data were collected (data accrual), whether the data as collected are complete, accurate and adequate for answering the question at hand (data adequacy), and whether the people and processes in place during data collection and analysis provide adequate assurance that bias is

minimized and data quality and integrity are sufficient (data assurance). FDA will consider existing data accrual and analysis infrastructure and methodology, as the fitness of a given data source is evaluated.

(1) Data accrual

A prospective protocol 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 utility and outcome assessments (i.e., common temporal framework) is essential to ensure reliability. Key factors FDA will assess include:

a. the preparedness of individual sites for complete and accurate collection of observational data (e.g., defined processes, site training and support, dedicated qualified personnel);

b. use of a common data capture form;

c. use of a common definitional framework (i.e., data dictionary);

d. adherence to a common temporal framework for collection of key data points;

e. the data collection procedures, data evaluation protocol or statistical analysis plan including when the data collection procedures were developed relative to actual data evaluation (i.e., prospective vs. retrospective);

f. 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 device, linkage to claims data);

g. patient selection and enrollment criteria that minimize bias and ensure a representative real-world population (e.g., all-comer's design, consecutive patient enrollment);

h. the timeliness of data entry, transmission, and availability;

i. whether the act of collection of data impacts the ability to measure treatment outcomes; and

j. whether necessary and adequate patient protections were in place (e.g., de-identified data, maintenance of 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 sources. To ensure sufficient reliability, data sources will also be evaluated with respect to 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:

a. assessments of data quality (e.g., abstracted from verifiable source);

b. adherence to source verification procedures and data collection and recording procedures for completeness and consistency;

c. completeness (i.e., minimized missing or out of range values);

d. data consistency across sites and over time;

e. evaluation of on-going training programs for data collection and use of data dictionaries at participating sites;

f. evaluation of site and data monitoring practices; and

g. the use of data quality audit programs.

The repurposing 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 determine data accuracy and authenticity. Comparing data from traditional clinical research to source documents through audits (i.e., external consistency) is an essential additional step in verifying the accuracy and completeness of the data. This type of verification is equally important for RWD that is intended to be used for regulatory analyses.

Regardless of the original purpose for collection of the RWD, requirements for data collection and quality assurance should be put into place during the data source design and development stages to optimize the reliability, quality and usefulness of the data. The data collection procedures should be clearly defined and described in a detailed data management standard operating procedures (SOP) manual. Standardizing procedures to ensure the use of uniform and systematic methods for collecting and cleaning data are vital to ensuring data quality. Adherence to the data quality assurance and control policies and procedures will be assessed.

VI. Examples Where RWE Can be Useful

The following examples are generalized from actual regulatory uses of RWE for 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 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 data on consecutive patients and focused on quality assessment/performance improvement data related to real-world procedures and device use outcomes, an IDE is not required for routine data collection operations, even though a substantial volume of data is generated from use of a device, including data on use outside of the cleared or approved indications for use.

Another example is a Class III device with a narrowly defined indications for use that over time, has seen an expansion in clinically accepted use that is outside of the approved indications for use. In this example, recent technological advances in the design of these devices have also led to their rapid and widespread use for a new set of clinical applications that are not described in the approved labeling. There is little published data to support the effectiveness of this use that is outside of the approved indications for use, while there are recently published reports of high rates of adverse events with the use of the devices for any indication for use. To address the lack of data to support new indications for use for this device, relevant medical societies have established a national registry to collect safety and effectiveness information for all patients implanted with this specific Class III device at participating institutions. 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 collection of specific follow-up data that might not otherwise be performed as part of standard medical care. FDA is hopeful that the data may address critical safety questions related to the use of these devices and may be of sufficient quality to help support labeling changes or other regulatory decisions for this device.

B. Postmarket Surveillance Studies (Section 522)

FDA has issued a series of postmarket surveillance study orders, related to investigating patient safety issues in a type of class II device, under the authority of Section 522 of the Federal Food, Drug, and Cosmetic 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 needed data to address the public health questions. The resultant registry was designed to collect data on all patients with the condition, including those treated with the devices of interest, other devices, and through medical management, and to follow their treatment outcomes. 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 data 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 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 to10 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 data 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 a registry exist that is capable of addressing the questions for which a Post-Approval Study (PAS) may be issued, FDA instead may issue a condition of approval that a manufacturer participate in and support collection/reporting of registry data on their device in lieu of a condition of approval specifying a formal PAS.

For example, a new breakthrough Class III medical device was recently approved based on prospective randomized controlled clinical trial data. Early in the PMA review process, the manufacturer began to consider postmarket commitments, and reached out to FDA, the Centers for Medicare & Medicaid Services (CMS), and the relevant clinical professional society. A registry was launched that provided data to support FDA and CMS data requirements and national quality assessment programs, in addition to the primary clinical quality assurance purpose desired by the clinical community. This registry has since been used to a) collect surveillance data on subsequent devices with similar designs and indications, b) collect and retrospectively analyze data 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 data on all uses of otherwise approved medical devices. The retrospective analysis of data from uses that are outside the approved indications for use did not require an IDE, but was reviewed by an IRB for human subject protection issues. However, prospective enrollment of new patients into a clinical trial using the registry infrastructure meets the definition of a Clinical Investigation and is subject to 21 CFR 50 (Informed Consent) and 21 CFR 56 (IRB Review). Additionally, if the prospective enrollment is considered significant risk and is being used to determine safety and effectiveness of a medical device, an IDE approval will be required.

D. Control Group

A manufacturer approached FDA during the development of a new medical device that had substantial technological changes from previous iterations of that specific device and other similar devices from other manufacturers. FDA determined that additional clinical evidence was needed to support an approval decision for this device. A registry exists that captures all uses of medical devices in this clinical indication. The manufacturer 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 sufficient data 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.

E. Supplementary Data

FDA evaluates available evidence to make the best decision for patients and public health. In the case where RWD has been systematically collected, FDA has used these data, in combination with case reports, publications, adverse event reports, engineering and nonclinical test data, and other sources of information available to FDA to provide a full understanding of the severity of the issue, precipitating factors, affected population and alternative therapies. Periodically, FDA identifies an issue related to the safety of a marketed medical device that was not detected in premarket trials. The addition of RWD has proven extremely valuable to FDA, patients, physicians, and manufacturers 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 that made interpretation of results difficult. A pre-existing observational registry collects and reports data on the control therapies. Subsequent analysis of these data supplemented the clinical trial data and assisted in the interpretation of the data, allowing FDA to come to an appropriate regulatory decision without requiring additional clinical trial data, precluding delays in regulatory decision-making. 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 by FDA for the review and comparison of safety or effectiveness endpoints[19]. An OPC is usually developed when device technology has sufficiently matured and can be based

[19] See 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.

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 by FDA 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 mature for use of a PG as for an OPC, and the data used to generate a PG is not considered as robust as that used to develop an OPC. A PG might be considered for challenging patient populations or if there is no clinical equipoise for any control. From a sufficiently relevant and reliable observational data 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 observational data.

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 Federal Food, Drug, and Cosmetic Act, related code or regulation, or 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.[20]
- **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.[21]
- **Electronic Health Record (EHR)—**An electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization. [22]

20 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

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

22 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

- **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.[23]

- **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]."[24]

- **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.[25]

- **Observational Study**—In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions, which can include medical products such as devices, or procedures as part of their routine medical care, but participants are not assigned to specific interventions (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.[26]

- **Prospective Study**—A prospective study (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.[27]

- **Real-World Data (RWD)** is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries). The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.

- **Real-World Evidence (RWE)—**RWE is the evidence derived from aggregation and analysis of RWD elements.

23 Ibid
24 Strom, Brian. Pharmacoepidemiology. Chichester, England: John Wiley and Sons, 2005.
25 Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions: Workshop in Brief 2015, Institute of Medicine
26 Adapted from https://www.clinicaltrials.gov/ct2/about-studies/glossary
27 Ibid

- **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.[28]

- **Retrospective Study**—A retrospective study (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.[29]

- **Surveillance**—Surveillance is a continuous and systematic process of collection, analysis, interpretation, and dissemination of descriptive information for monitoring health problems[30]. Postmarket surveillance is the active, systematic, scientifically valid collection, analysis and interpretation of data or other information about a marketed device.[31]

- **Traditional clinical trial**—Traditional clinical trials are typically conducted in specialized research settings and with specific populations, that often utilize measures designed to control variability and ensure data quality, such as lengthy 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 may also include substantial efforts to assure compliance with treatments and avoid concomitant treatments that might influence the randomized treatment effect.

28 Registries for Evaluating Patient Outcomes: A User's Guide
29 Ibid
30 JW Buehler. Surveillance (Ch. 22) pages 435-458 in KJ Rothman & S Greenland (editors) Modern Epidemiology 2nd edition. Philadelphia: Lippincott-Raven Publishers, 1998
31 21 CFR 822.3