



Real-World Clinical Evidence Generation: Advancing Regulatory Science and Patient Access for *In Vitro* Diagnostics (IVDs)

**A Framework for Incorporating Real-World
Data and Evidence Into Pre- and Postmarket
Regulatory Decision-Making for IVDs**

**A report of the IVD Real-World Evidence Working Group
of the Medical Device Innovation Consortium (MDIC)**

Table of Contents

Table of Contents	2
Authors	4
Disclaimer	5
About the Medical Device Innovation Consortium (MDIC)	6
Executive Summary.....	7
SECTION 1	Introduction..... 10
	1.1 Scope of the Framework..... 10
SECTION 2	Defining Real-World Data and Real-World Evidence 11
	2.1 RWD Generation From Various Sources..... 11
	2.2 Collection of RWD for IVDs..... 12
	2.3 Use of IVD RWE for Regulatory Assessment 12
SECTION 3	Uses of Real-World Evidence Across the IVD Total Product Life Cycle (TPLC)..... 14
	3.1 Potential Value of Real-World Evidence Across the TPLC..... 15
SECTION 4	Uses of Real-World Evidence: Research and Development 15
SECTION 5	Uses of Real-World Evidence: Premarket Decision-Making 16
	5.1 Premarket Authorization or Notification..... 16
	5.2 Measures of Clinical Performance 16
	5.3 Basic Study Design Considerations 17
	5.4 Suitability of RWD for Various Types of Clinical Validation Studies... 18
	5.5 Virtual Clinical Performance Study Using RWD 20
	5.6 Examples of RWD Use in Premarket Decision-Making..... 21
SECTION 6	Premarket Regulatory Assessment and Real-World Evidence..... 27
	6.1 Regulatory Considerations 27
	6.2 Clinical Considerations 27
SECTION 7	Use of RWD in Postmarket Decision-Making 28
	7.1 Postmarket Surveillance 28
SECTION 8	Strengths and Limitations of Real-World Data..... 28
	8.1 General Strengths and Limitations of RWD 28
	8.2 Systematic Bias 30
	8.3 Missing Data 30



SECTION 9	Real-World Data Relevance	31
	9.1 Assessing Data Relevance	31
SECTION 10	Appendices	32
	10.1 Appendix A: Examples of IVD Regulatory Assessment Using Real-World Evidence	33
	10.2 Appendix B: Glossary	34
SECTION 11	References	39



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Disclaimer

The general recommendations in this document:

- *Do not imply FDA concurrence for specific applications*
- *Do not represent the opinion or policy of the FDA*
- *Do not include any specific recommendations to the FDA regarding how to review collected RWD or how to use RWE to support regulatory decisions for IVDs*
- *Are not a substitute for FDA Guidance documents or for direct engagement with the CDRH staff regarding the incorporation of RWE into the regulatory decision-making process for a given IVD*

To obtain feedback from the FDA concerning a specific device, a pre-submission may be submitted per the FDA Guidance "Requests for Feedback on Medical Device Submissions: The Q-Submission Program and Meetings with Food and Drug Administration Staff,"¹ or a general question may be submitted to CDRHClinicalEvidence@fda.hhs.gov. The FDA is committed to providing timely, least-burdensome feedback that will accelerate the process to a regulatory decision that will enable safe and effective medical devices to get to market.

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About the Medical Device Innovation Consortium

The Medical Device Innovation Consortium (MDIC) is the first public-private partnership created to advance the medical device regulatory process for patient benefit.

MDIC was formed in 2012 to bring the FDA and industry together to share vital knowledge that can help bring safe, affordable, and effective devices to patients and providers more quickly. MDIC membership and participation is open to nonprofit, industry, and government organizations that are substantially involved in medical device research, development, treatment, or education; or in the promotion of public health; or that have expertise or interest in regulatory science.

MDIC is designed to pursue several strategies that support its mission:

- Create a forum for collaboration and dialogue
- Make strategic investments in regulatory science, utilizing working groups to identify and prioritize key issues, and to request, evaluate, and implement project proposals
- Provide and enable implementation of tools from these projects that drive cost-effective innovation

The activities and outputs from MDIC are intended to:

- Ensure that innovative technology is readily available to U.S. patients
- Provide industry and government with methods and tools that may be used to expedite medical device development and the regulatory process
- Reduce the risk and expense of clinical research
- Reduce time and cost of medical device development

MDIC members provide guidance and leadership through collaboration to develop solutions for regulatory, scientific, health, and economic challenges within the medical device and diagnostic industry.

MDIC Clinical Diagnostics (ClinicalDx) Program

MDIC’s Clinical Diagnostics (ClinicalDx) program provides a collaborative environment to drive the creation of tools and methods based on science to reduce unnecessary delays and costs to improve the delivery of better diagnostic tests to help patients. This program includes technically and clinically focused projects:

Sample Projects in the ClinicalDx Program

Technically Focused Projects	Clinically Focused Projects
<ul style="list-style-type: none"> • Surrogate Samples https://mdic.org/project/surrogate-samples/ • Fingerstick Capillary Blood Specimens https://mdic.org/project/fingerstick-capillary-blood-specimens/ • Cancer Genomic Somatic Reference Samples https://mdic.org/project/cancer-genomic-somatic-reference-samples/ 	<ul style="list-style-type: none"> • IVD Clinical Evidence https://mdic.org/project/ivd-clinical-evidence/ • IVD RWE (current framework) https://mdic.org/project/ivd-real-world-evidence/



Executive Summary

The MDIC *In Vitro* Diagnostic (IVD) Real-World Evidence (RWE) Framework (“Framework”) was established following the release of the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) Guidance, “*Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food and Drug Administration Staff*,” (hereinafter “*RWE Guidance*”), which focuses on the use and potential value of RWE to support regulatory decision-making for medical devices.² In the *RWE Guidance*, the FDA notes that such evidence may be created from real-world data (RWD) through the use of appropriate methods and recommends that parties wishing to use RWE contact the FDA regarding the submissions using RWE. The Framework builds off of this by providing additional contextual information to help industry and the FDA consider when and how RWD, appropriate designs, and statistical methods including modeling to generate RWE might be incorporated into product development and regulatory decision-making, particularly in support of clearance or approvals of IVDs. Although RWE has been used by the FDA for years in many different contexts across the Total Product Life Cycle (TPLC), there is less experience with RWE across the range of IVD devices, especially in premarket regulatory decision-making.

This framework focuses on issues pertinent to clinical validation of RWD in **premarket and postmarket** regulatory decision-making of IVD devices.

To oversee this project, MDIC formed an IVD RWE Working Group consisting of interested participants among MDIC’s member organizations supplemented with experts in regulatory science and policy, epidemiology, and biostatistics from government and other organizations. For a list of the Working Group members, please refer to the Authors page at the beginning of the Framework.

This Framework contains a summary of all elements of the Working Group’s approach. Additional content can be found at <https://mdic.org/project/ivd-real-world-evidence/>.

Purpose of the IVD RWE Framework

This Framework is intended to help stakeholders navigate their way through obtaining and using “fit-for-purpose” RWD/RWE by addressing:

- 1) What IVD RWD are
- 2) How IVD RWE is generated
- 3) Whether or not to incorporate RWE into premarket regulatory decision-making for IVDs
- 4) How to use RWE, when appropriate, for premarket and postmarket regulatory decision-making for IVDs
- 5) Specific considerations applicable to use of RWE for IVDs in this context

Key Points Emphasized in the Framework

Important takeaway points from the Framework include:

- **Collecting and using RWD can help manufacturers and the FDA ensure that the safety and effectiveness of IVDs are appropriately representative of the target patient population (an intended use population) and medical practice using the IVD device.** Relative to data from clinical studies, data generated and analyzed from routine clinical practice can be used to support the safety and effectiveness

of an IVD device for new intended uses and provide additional information about safety and effectiveness of the IVD device in postmarket settings.

- **Fundamental evidentiary requirements are risk based, regardless of origin of the evidence. The use of RWD and RWE does not change the process for FDA premarket review of IVDs.** The FDA requires valid scientific evidence (VSE) to provide reasonable assurance of safety and effectiveness, regardless of the source of the data. RWE can be the source or a supplement to other safety and effectiveness or substantial equivalence data but does not purport to change the existing regulatory requirements and evidentiary needs.
- **RWD can be generated across the TPLC.** IVD development requires a life-cycle approach, with product evaluations and modifications continuing to occur even after a product reaches the market. RWD generated throughout this process can be considered for evaluation in regulatory decision-making. RWD generated in countries outside of the United States (U.S.) can be used in U.S. regulatory decisions if the relevance can be appropriately addressed using reliable RWD in the context of the benefits and risks posed by the IVD.
- **RWE is not a requirement for IVD marketing applications (e.g., PMA, 510(k), De Novo, HDE, etc.) to the FDA, but it can be a valuable element of an overall regulatory strategy.** The collection of RWD and submission of RWE can be considered as part of an overall regulatory strategy and may reduce costs and time when compared with evidence generated through clinical studies. In turn, this may decrease the time it takes to bring innovative IVD devices or uses to patients and healthcare providers. As electronic RWD infrastructure improves to become more harmonized and interoperable, this can significantly reduce the burdens associated with collecting key data elements and validating data quality.
- **Careful consideration is required in determining when and how to select appropriate RWD for IVDs, apply appropriate study designs and statistical methods, and interpret results accordingly and within the scope of the evidentiary needs of the regulatory submission.** Fundamentally, regulatory decisions must be supported by VSE; the FDA encourages a “least-burdensome” approach to providing VSE for IVDs whether that comes in the form of RWE or evidence from clinical studies, including those using prospectively collected samples, archived specimens, leftover samples, and surrogate samples (occasionally). For additional information, please refer to FDA guidance.³ RWD are considered observational by their nature as they are generated during routine clinical encounters and reflect real-world clinical practice.² Appropriate data validation, including assessment of relevance and reliability, should be made to aid the FDA in decision-making with RWE. It would be prudent for sponsors to discuss plans with the FDA early in the regulatory assessment process if they plan to submit RWE. For additional information on the Pre-Submission process, please refer to FDA’s Guidance “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff.”¹

This Framework should be considered an initial thought piece outlining considerations for how industry and the FDA might evaluate RWE for IVDs in the premarket and postmarket regulatory decision-making process and will thereby encourage continued growth and maturation of this field. It is intended to be an initial ideation that outlines a range of considerations of how the FDA and parties interested in using RWE might incorporate RWE into the premarket regulatory decision-making process. It is not intended to be prescriptive, nor does it purport to be a definitive document about incorporating RWE into a regulatory strategy.

MDIC and the IVD RWE Working Group welcome constructive feedback on this Framework and ideas for further work in the field of RWE use for regulatory purposes.



Sections 1-9: Real-World Clinical Evidence Generation: Advancing Regulatory Science and Patient Access for *In Vitro* Diagnostics (IVDs)

**A Framework for Incorporating Real-World
Data and Evidence Into Pre- and Postmarket
Regulatory Decision-Making for IVDs**

SECTION 1

Introduction

RWE has potential to support premarket regulatory decision-making for IVDs when it meets FDA requirements. The Code of Federal Regulations 21 CFR 860.7(c)⁴ states that “although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only VSE to determine whether there is reasonable assurance that the device is safe and effective.”⁴ For IVDs, safety and effectiveness typically are shown through VSE establishing analytical validity and clinical validity. If considered VSE, RWE may help establish or support clinical validity or analytical validity.

Use of RWE is not new to the FDA. However, its broad application is often not well understood. As technology advances and healthcare data become more digitized and electronically transmissible, the use of RWD is expanding. The 21st Century Cures Act (Act) (section 3022⁵) directed the FDA to establish a program to evaluate the potential use of RWE for regulatory decision-making. The Act includes interoperability (section 4003⁵) and electronic health record (section 4005⁵) provisions that have the potential to improve access to RWD for devices, including IVDs, in addition to pharmaceuticals.

Use of RWE in regulatory decision-making for IVDs has some unique considerations as its regulatory assessment is different than therapeutics (e.g., randomized controlled trials are usually not used for clinical validation of IVD devices; leftover or surrogate samples may be used in some cases). There remains a unique opportunity to develop best practices, tools, and methodologies specifically for the acquisition and appraisal of relevant IVD data generated through routine clinical practice, such that it can be evaluated with scientific rigor and meets the necessary parameters for data quality assurance to support regulatory decisions.

Informed by an analysis of current and historical experiences, this Framework describes when and how appropriate study designs and analytical methods may be applied to relevant and reliable RWD to generate valid scientific RWE to inform or augment regulatory decisions in support of clearance or approval of an IVD. It discusses general study design and methodology considerations when making regulatory decisions based on data generated from a routine clinical environment, including addressing data quality issues (e.g., missing data, transparency in data generation processes, systematic biases) and approaches to establishing criteria for data evaluation in a benefit/risk context. The Framework also describes both hypothetical and previously approved regulatory case examples of applications of RWE in the IVD setting, such as when data for clinical validation may be difficult or burdensome to collect.

1.1 Scope of the Framework

Device manufacturers often leverage online resources (websites and social media platforms) to identify potential participants for clinical trials. These outreach efforts provide opportunities to communicate institutional review board (IRB)-approved benefit and risk information to patients.

This Framework identifies:

1. The current RWD and RWE landscape for IVDs, including:
 - a. RWD sources for IVDs
 - b. Challenges and barriers to applying RWE for IVD regulatory decision-making
2. Potential applications of RWE in support of IVD premarket regulatory decision-making
3. Potential applications of RWD in support of IVD postmarket issues

4. A proposed approach to evaluate relevance and reliability of RWD to assess data fitness for IVD regulatory decisions
5. Study designs and methods to generate potentially regulatory-grade (i.e., VSE) RWE for IVDs

This Framework further clarifies varying terminologies across many sources and addresses distinctions between IVDs and other medical devices/products (e.g., therapeutics). It highlights that regardless of the context (i.e., diagnostic or therapeutic), data should be collected, aggregated, stored, and accessed in compliance with applicable laws, regulations, and policies, including 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. Focus is placed on the application of RWE specific to IVDs but does not comprehensively address how to access or evaluate RWD sources for relevance or reliability, which can be highly nuanced based on the IVD under consideration. The National Evaluation System for health Technology Coordinating Center (NESTcc) is focusing on addressing and streamlining these processes. For more information, visit: <https://nestcc.org>. Note that some important RWD/RWE considerations are not unique to IVDs. This Framework is also not intended to address RWE for the broader biotechnology ecosystem, although some aspects may be pertinent.

SECTION 2

Defining Real-World Data and Real-World Evidence

FDA's RWE Guidance,² which has been echoed by others,⁶ defines RWD and RWE as follows:

- **“Real-World Data (RWD)** are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources.”²
- **Real-World Evidence (RWE):** More specifically in the regulatory context, FDA defines RWE as “clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.”²

Across the spectrum of application for RWE, regulatory decisions can only be made based on VSE that is fit for purpose, that is, sufficiently reliable and relevant RWD. RWD relevance and reliability are typically established by demonstrating that the data attained have been appropriately curated and validated, appropriate study design and methods of data analysis have been selected, and data provenance and traceability can be assessed when interpreting results. Traceability is supported by the ability to track data each step of the way back to the point of provenance, with a full understanding of any modifications of that data that may have occurred. Many of the IVD-specific factors are discussed throughout this IVD RWE Framework in order to help guide the end user through the submission of supportive RWE to the FDA.

2.1 Real-World Data Generation from Various Sources

Real-world data for IVDs can stem from several sources, both public and private, including but not limited to:

- Electronic health records (EHRs)
- Laboratory information systems (LISs)
- Administrative claims databases
- Hospital discharge databases



- Disease registries
- Medical device registry
- Image databases and repositories
- Patient-reported outcomes (PROs)
- Death indexes
- Public health databases (e.g., Centers for Disease Control and Prevention)

Generation of VSE might involve collection, aggregation, and analysis of data from multiple individual real-world data sources.

2.2 Collection of Real-World Data for IVDs

RWD for IVDs can be prospectively or retrospectively collected data. Currently, most RWD are retrospectively collected; however, as the transmission of interoperable de-identified information becomes more routine, other means of prospectively collecting information may offer useful opportunities in the TPLC evolution of a device.

As most RWD are currently retrospectively collected, this document will focus on the generation of data without a specific research question in mind. An important strength of such retrospectively collected data is that they allow evaluation of healthcare utilization as it occurs in routine medical care encounters. In many instances, this can also offer larger study populations and longer periods of observation or follow-up (e.g., longitudinal data), enabling investigators to explore specific heterogeneous subpopulations and outcomes.

Collecting and using RWD can be a least-burdensome approach to generating necessary evidence across the TPLC, including to support regulatory submissions, as it is typically retrospectively analyzed. In some instances, these data may produce results similar to prospective clinical studies. However, given that such data are often not collected for the explicit purpose of research, several limitations may exist, including inaccurate recording of health or disease events, systematic biases, missing data or variables of interest including unique device identification, insufficient clinical details or temporal certainty about use of a specific IVD, and opaque reporting of data collection and management, including an inability to establish data provenance (an important step in evaluating data quality).^{7,8}

2.3 Use of IVD Real-World Evidence for Regulatory Assessment

IVDs (and other medical devices) are classified into one of three classes – Class I, II, or III – based on their risks and the regulatory controls necessary to provide reasonable assurance of safety and effectiveness. Class I devices generally pose the lowest risk to the patient and/or user and Class III devices generally pose the highest risk. Before a Class II or III device can be marketed, unless otherwise exempted, the FDA requires regulatory submissions that include VSE demonstrating substantial equivalence to a legally marketed predicate device (Class II devices reaching U.S. market via 510(k) pathway are considered cleared) or reasonable assurance of safety and effectiveness (Class III devices reaching U.S. market via Premarket approval [PMA] process are considered approved.) Also, a humanitarian device exemption (HDE) application may be submitted for humanitarian use devices, which are intended to benefit patients with a disease or condition that affects fewer than 4,000 individuals in the U.S. per year.



For IVDs, the requirements for submitted data can vary depending on the disease intended for diagnosis, classification, and risk to patients associated with the IVD. Least-burdensome⁹ approaches and risk-based regulatory decisions are assumed, including those that include RWE where appropriate. Following premarket review, each IVD is also assigned a Clinical Laboratory Improvement Amendments (CLIA) categorization to determine in what type of environment the IVD can be used (i.e., high-complexity lab settings, moderate-complexity lab settings, CLIA-waived settings, or over-the-counter), based on the evidence that they can be appropriately used in each setting.

While IVD RWD are typically collected for non-regulatory purposes, their use in RWE generation may constitute VSE that can streamline the process for bringing innovative new technologies to market while maintaining the standard of reasonable assurance of safety and effectiveness of IVDs. In the RWE Guidance,² the FDA noted that RWE may be valuable for regulatory decision-making (applicable to therapeutic and diagnostic devices), for example:

- In settings where clinical studies are impractical to conduct (e.g., rare diseases, long follow-up needed to achieve endpoint(s), cost)
- For filling important evidentiary gaps not typically addressed with traditional clinical studies
- When allowing sponsors to generate evidence in support of an effectiveness claim that is potentially useful to multiple stakeholders, regulators, patients, and the public
- For potentially reducing time and cost of evidence development for regulatory decisions

A wealth of RWE covering IVD experience exists and is routinely collected in the course of treatment and management of patients. In addition to facilitating potentially rapid access to innovative IVD technologies, the value of RWE is the inclusion of data from heterogeneous patients with a wide range of characteristics, experiences, comorbidities, and treatment protocols. RWD may also include pre-analytical variables (e.g., specimen collection containers, sample storage, and handling).

RWE may also offer advantages in diseases or outcomes with low prevalence and limited availability of specimens, where test performance can be supported by a small number of samples and/or the use of surrogate samples. However, data collected throughout the course of routine clinical care may not have the same traceability as data collected within a clinical study setting. Additionally, key social and demographic data may not have been documented, linked, or be accessible to allow necessary analyses. Even so, under certain circumstances, these sources of RWE may be of sufficient quality to inform or augment the FDA's understanding of the benefit-risk profile of IVDs at various points in their life cycle.

Among other uses, RWD from a wide variety of data sources from routine clinical encounters can be used in place of, or as a supplement to, data from clinical studies to determine IVD safety and effectiveness, and the risk/benefit profile of a device. However, not all RWD are of appropriate quality, and not all RWE is fit for use in regulatory submissions to the FDA in support of clearance, approval, licensing, authorization, for example.

SECTION 3

Uses of Real-World Evidence Across the IVD Total Product Life Cycle (TPLC)

The FDA’s Center for Devices and Radiological Health (CDRH) uses a TPLC model to illustrate the iterative nature of medical device design and development (Figure 1).

IVD Total Product Life Cycle Approach

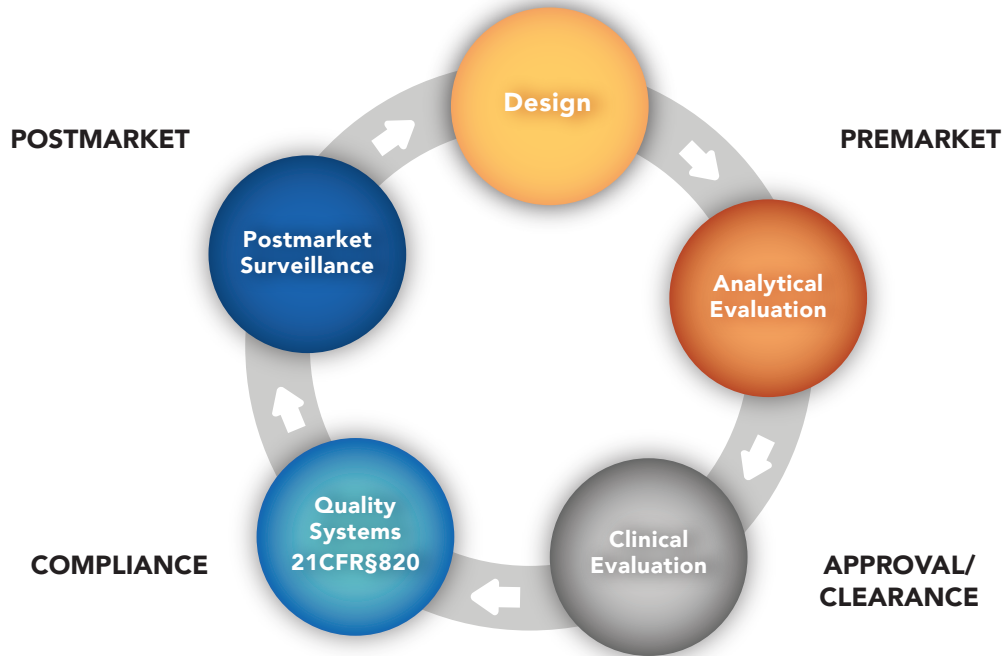


Figure 1. The Total Product Life Cycle (TPLC) approach to IVD medical device development and regulation. Medical device development is an iterative process that rapidly incorporates analytical, clinical, and manufacturing experience into next-generation concept and design. RWD can be generated and RWE applied across the IVD TPLC.

Like other devices, IVD development is an iterative approach, with a large portion of the IVD’s TPLC occupied by product development from concept to marketing. Although typically portrayed as a compartmentalized process with distinct phases, such as analytical validation and clinical validation, steps in IVD development overlap, and portions may need to be repeated as testing and user experience are incorporated into product modifications and the IVD moves closer to its marketed form. Product evaluations and modifications continue to occur even after a product reaches the market.

RWD may be generated and RWE used throughout the IVD TPLC; exactly how RWE may support or contribute to decision-making will depend upon the IVD and the evidence needs at a particular stage.

3.1 Potential Value of Real-World Evidence Across the TPLC

IVD RWE can be used throughout the IVD TPLC, with particular value in premarket regulatory decision-making for clearance and approvals. With appropriate application of carefully selected study design methodologies and analyses, RWE can inform product development, outcomes research, patient care, clinical utility, research on health systems, quality improvement, surveillance, and well-controlled safety and effectiveness studies.⁸ This evidence can also provide further insights into how factors such as clinical settings, providers, or health system characteristics will influence selection of a given diagnostic, treatment, effect, or health outcomes.

SECTION 4

Uses of Real-World Evidence: Research and Development

RWE can be used to assess the potential for new IVDs or IVD uses, or to support modifications to existing IVDs. Possible uses include, but are not limited to:

- Site or patient identification – for enrollment in clinical studies
- Feasibility studies – to test protocols for new products or a potential new intended use
- Selection of historical control, comparator, or predicate device(s) for clinical study
- Quality improvements – surveillance of specific postmarket IVD performance factors
- Meeting design control requirements – for example, RWD could be used as design input for new product development
- New uses and expanded indications for IVD devices – safety and effectiveness of an assay outside of its intended use (i.e., “off-label” use), extending indications to other patient populations, tissues, or sample types; RWE can provide evidence for identifying and supporting new claims or otherwise expanding the labeling of an IVD
- Methods selection – use of RWD to simulate clinical trial results or outcomes of testing prior to implementing a costly clinical trial
- Review and comparison of safety and effectiveness endpoints – Objective Performance Criteria and Performance Goals derived from clinical studies and/or registries may be used
- Redefining current use models, for example, to define new scoring methods in histology or to define new cutpoints for existing assays

The data available may be specific to the IVD under development, or it may be associated with a similar IVD for the same intended use, such as a test measuring the same analyte. For example, data generated by labs may be available inpatient management records or non-registrational therapeutic study data as RWD.

SECTION 5

Uses of Real-World Evidence: Premarket Decision-Making

RWE can be valuable in the clinical validation phase of the TPLC. RWE use cases may include:

- Evidence to identify, demonstrate, or support the clinical validity of an IVD device
- Generating performance characteristics as clinical sensitivity and specificity
- Evidence to support an Investigational Device Exemption (IDE) submission for a significant risk IVD

5.1 Premarket Authorization or Notification

RWE may be used to support a petition for reclassification of a medical device under section 513(e) or (f)(3) of the Food Drug & Cosmetic Act, approval of a Humanitarian Device Exemption (HDE), approval of a Premarket Approval Application (PMA), granting of a De Novo request, clearance of a Premarket Notification (510(k)), or a modification to an existing IVD subject to clearance or approval.

Many IVDs require prospective clinical data collection or the use of well-characterized archived specimens to support clinical validity. The traditional approach to clinical validation data collection and evaluation can be costly and time consuming and may not capture the heterogeneity of real-world populations. However, the FDA recognizes that VSE may include RWE. RWE may supplement data prospectively collected from clinical studies, or in some circumstances provide sufficient VSE independently to inform regulatory decisions, speeding access to innovative IVDs that are analytically and clinically valid. For example, data generated by CLIA-certified laboratories to validate an assay for a new intended use and RWD that reveals performance of an IVD for that use, can be leveraged to support product submissions for the new use. In addition, many IVDs are launched outside the U.S. prior to seeking approval to market the product in the U.S. Routinely generated data collected in real-world settings outside the U.S. may be useful to inform regulatory decisions in the U.S., including premarket approvals, notifications, authorizations, and licensing. For additional information regarding the acceptance of medical device clinical data generated outside the U.S., please refer to FDA's Guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."¹⁰

5.2 Measures of Clinical Performance

There is a wide variety of IVD devices, for example qualitative (binary or with multiple outputs), semi-quantitative, quantitative, titered, and assays with algorithmic analyses (IVD devices based on artificial intelligence/machine learning), as well as software and instruments, among others. Measures of clinical performance depend on the type of the IVD device and the intended use/indication for use claim for this device.

5.3 Basic Study Design Considerations

The list below is not intended to be exhaustive and at minimum should be considered in study design.

- Ideally, for clinical performance studies where there is an established gold standard, each subject should have results from the candidate test and from the gold standard (a best available method for determination of the clinical status). Some devices require only an analytical accuracy study with clinical specimens; in this case, each subject should have a result from both the candidate test and an appropriate comparator method (e.g., a method traceable to internationally accepted standards). Tests should be performed on aliquots of the same sample in a similar time frame, if possible.
- Ideally, information about candidate test results should not be used in the determination of gold standard results (clinical status). Generally, it is inappropriate to compare the results of the candidate test with the output of a testing algorithm that combines several comparative methods if the algorithm uses the outcome of the candidate test.
- It is inappropriate to discard equivocal, indeterminate, intermediate, or gray-zone candidate test results when calculating measures of clinical performance.
- It is important to understand the potential sources of bias so that they can be avoided or minimized through appropriate data element selection or data collection, study design, or analytical methods. The estimates of the clinical performance measures should be unbiased, and if bias is present, its impact on the strengths and limitations of observed inferences should be considered in the decision-making process about clearance/approval, taking into account risks and benefits.
- In general, for IVD tests used in routine clinical practice, referral to a clinical procedure to make a final determination of the clinical status is only undertaken for subjects with positive test results. For example, while positive predictive value (PPV) can be determined, test performance measures such as negative predictive value (NPV) typically cannot be determined without data on the clinical status of subjects with a negative test result.
- Using results from discrepant resolution alone is inadequate to estimate the clinical sensitivity and specificity of the candidate test. For details, see FDA Guidance “Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests.”¹¹

Ideally, RWD will reflect the clinical diversity for which the IVD is intended. While recognizing that subgroups may not be statistically significant, the data should be appropriately analyzed according to the variables relevant to the clinical question at hand. For more information, please refer to the FDA Guidance documents “Evaluation of Sex-Specific Data in Medical Device Clinical Studies” and “Evaluation of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies.”^{12,13}

5.4 Suitability of RWD for Various Types of Clinical Validation Studies

This section describes the potential suitability of RWD for various types of clinical validation studies. Clinical validation studies for IVD devices are either clinical performance studies or clinical outcome studies (interventional studies) (Table 1). Clinical performance studies can be either observational or non-observational.³

Table 1. Suitability of RWD for various types of clinical validation studies

TYPE/SUBTYPE OF STUDY		CHARACTERISTICS	SUITABILITY OF RWD
CLINICAL PERFORMANCE STUDIES	Observational Studies	No collection of additional samples by interacting or intervening with living people AND No additional procedures for determination of the clinical status (target condition) – clinical status is determined according to routine clinical practice	Yes
	Non-Observational Studies	Additional samples collected specifically for the study purposes OR Additional procedures performed for determination of clinical status OR both (additional samples and additional procedures)	No
CLINICAL OUTCOME STUDIES (INTERVENTIONAL STUDIES)		Study protocol requires patient management based on test results	No

An observational study is a study that does not involve any intervention on the part of the investigator (investigators observe without intervention other than to record, classify, count, and statistically analyze the data).

An IVD clinical performance study can be an observational study when it reflects routine clinical practice, when obtaining the candidate test results does not require collection of additional samples by interacting with living people, and when it does not require additional procedures for determination of the clinical status of subjects beyond routine clinical practice. RWD can be suitable for observational IVD clinical performance study designs, as explained in Sections 5.5 and 5.6. Examples of observational IVD clinical performance studies are shown in Figure 2.

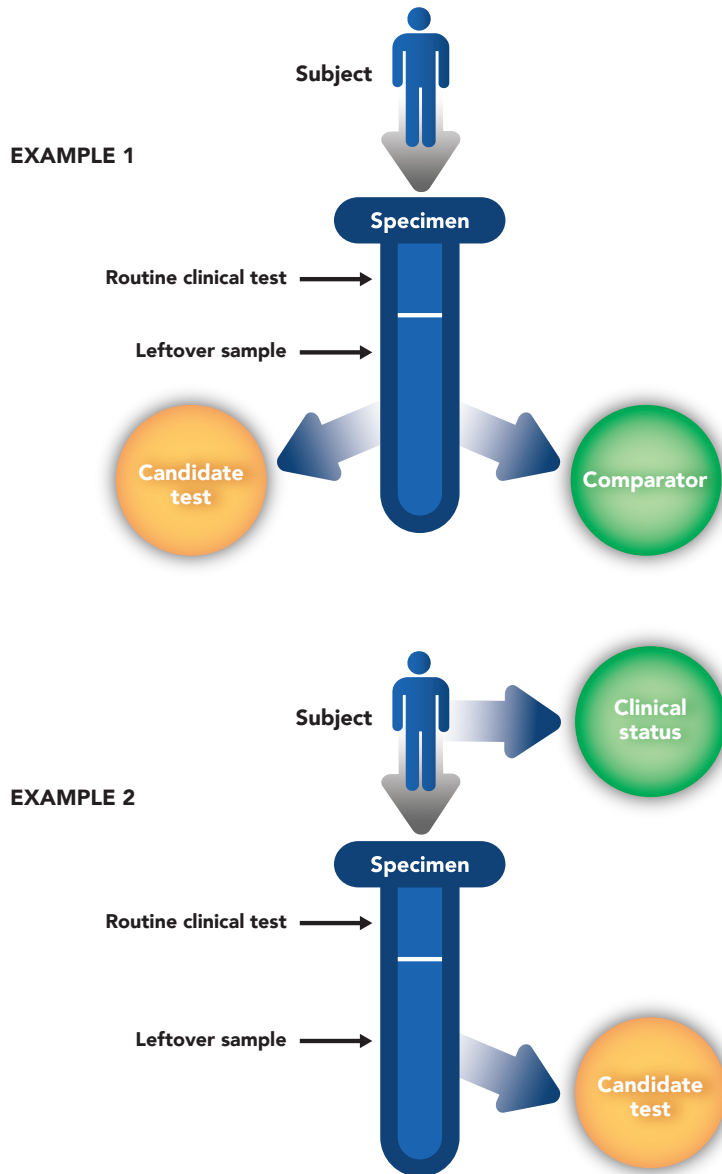


Figure 2. Examples of clinical performance studies that are observational. Example 1 demonstrates how to determine results of the comparator and candidate test using a leftover sample collected during a routine clinical encounter (e.g., gold standard or test performed in routine practice). Example 2 demonstrates that when the clinical status is known, a leftover sample may be used with the candidate test to determine test performance.

Frequently, IVD clinical performance studies are non-observational because unbiased estimation of the clinical performance of the IVD device requires a study design that includes either collection of additional samples, as shown in **Figure 3**, or when additional procedures for determination of the clinical status are performed beyond routine clinical practice. RWD is generally not suitable for non-observational clinical performance studies.

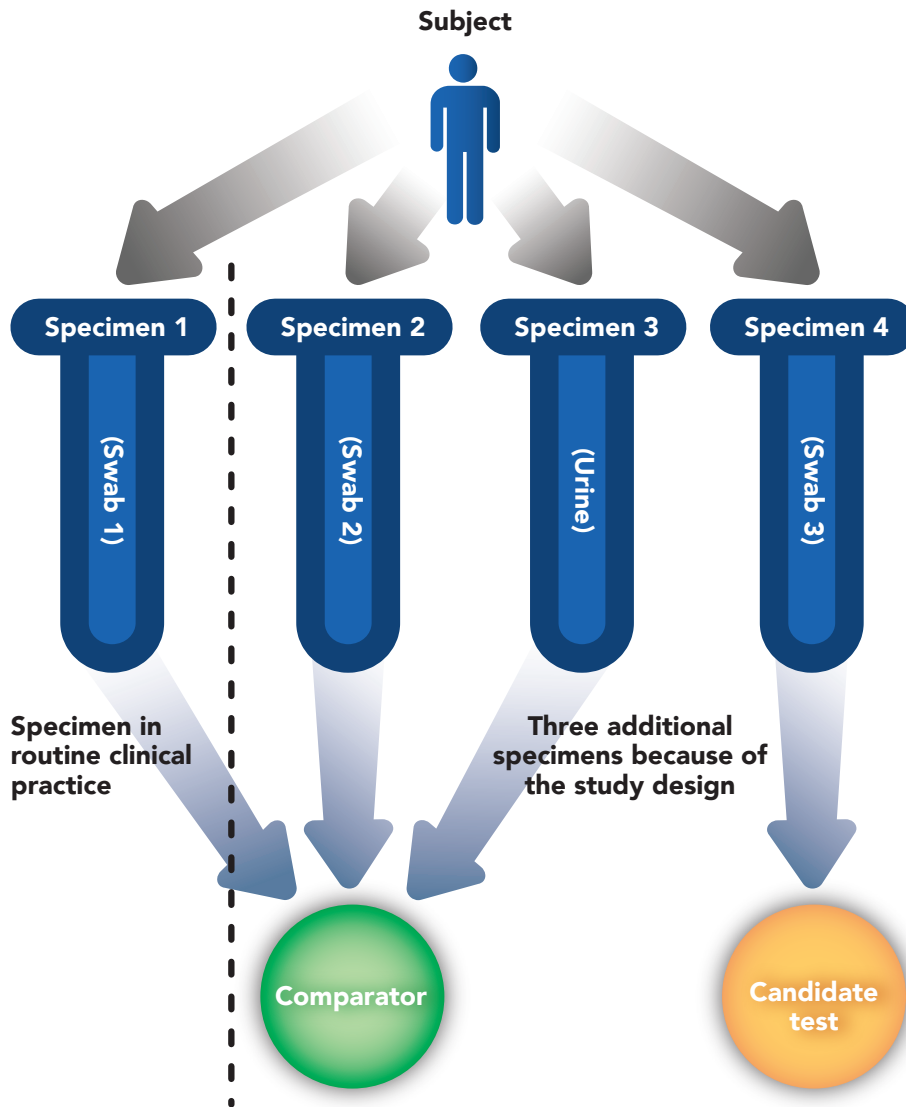


Figure 3. Example of a clinical performance study that is non-observational. Comparing known prospectively collected samples beyond those used to evaluate patient status in routine clinical care.

5.5 Virtual Clinical Performance Study Using RWD

RWD are observational by nature but can be used to mimic a clinical performance study for IVD clinical validation. To support this approach, a target population, study protocol, and methods for addressing biases should be developed. Because this study is observational and not conducted as a clinical performance study, we refer to it as a **virtual study based on the RWD**. Below are some examples of observational clinical performance studies using RWD to support premarket approval/clearance of an IVD device.

5.6 Examples of RWD Use in Premarket Decision-Making

RWD has a wide range of uses for premarket decision-making. The hypotheticals provided below reflect a few examples of observational clinical performance studies using RWD. They include how and when RWD might be used, with graphics illustrating potential data schemes.

Example 1: RWD and Virtual Clinical Performance Study coincide.

RWD

A binary qualitative IVD device is used outside the U.S. for detection of analyte X (e.g., a rapid test). According to routine clinical practice, *each* subject also has results obtained from the comparator method at a later time (e.g., three weeks later) (Figure 4).

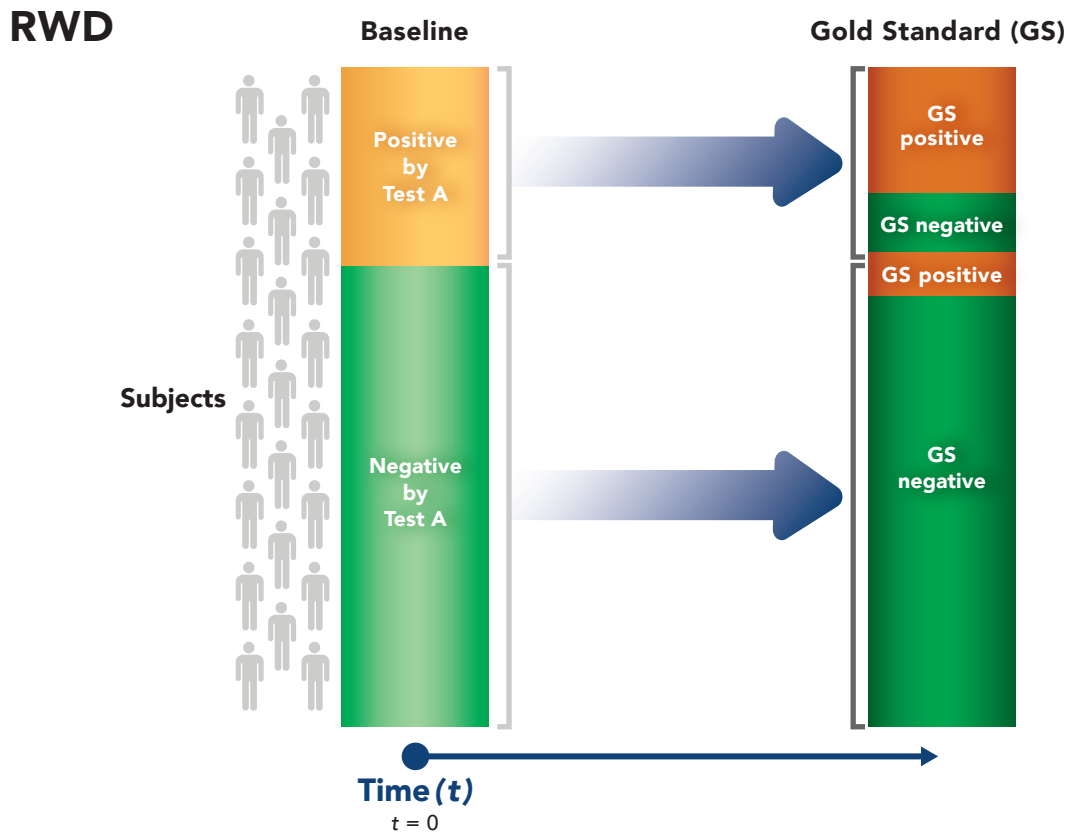


Figure 4. Example of a virtual clinical performance study. Patients are tested with a candidate test followed by a comparator test (e.g., gold standard) according to routine clinical practice.

If issues related to data obtained using an assay outside the U.S. are properly addressed (e.g., similarity in the target populations, clinical practice, screening intervals, levels of experience of the operators performing the test), RWD can be used for unbiased estimation of clinical sensitivity and clinical specificity. In this case, the virtual study coincides with RWD.

Example 2: RWD come from a binary “aid in diagnosis” IVD, and Virtual Study is for a “risk assessment/prognostic” claim.

RWD

- Binary qualitative IVD device is an approved/cleared test for the target population as an aid in diagnosis of the target condition (disease XYZ). In the current clinical practice, the IVD device is used according to the intended use: Subjects with positive test results are referred to the confirmatory procedures/tests and if the disease XYZ is present, this subject has an appropriate treatment (**Figure 5**).
- Subjects with negative test results have follow-up visits. Risks of the disease XYZ for the subjects with negative results is known from the clinical performance premarket study of the IVD device as “aid in diagnosis.”
- Subjects have information about follow-up visits and their clinical status.

RWD

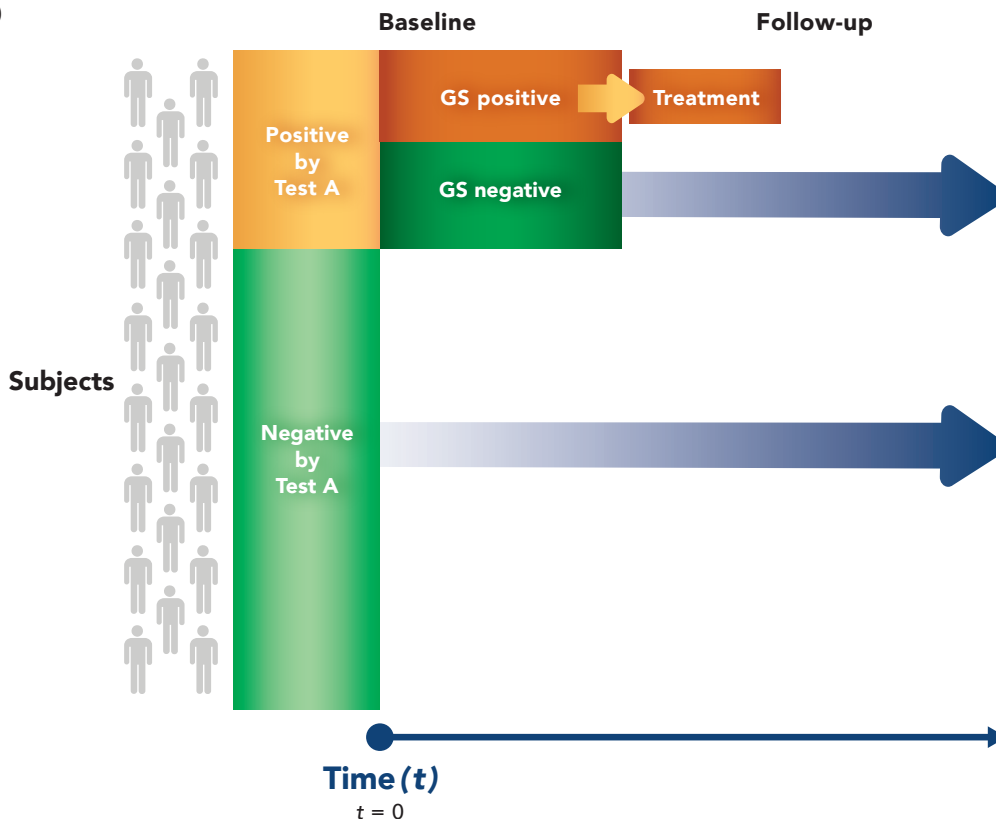


Figure 5. Scheme for RWD aid in diagnosis and follow-up. RWD are intended to demonstrate the claim extension of an “aid in diagnosis” IVD for risk assessment/prognosis of a given disease or target condition.



Virtual Study

Virtual study with “risk assessment/prognostic” claim:

- Target population is a *subset* of subjects of the RWD, subjects WITHOUT disease XYZ at the baseline.
- Follow-up RWD are used for estimation of the risk of disease XYZ for subjects with positive test results and with negative test results.
- Potential biases should be investigated, and an appropriate statistical analysis including modeling should be performed in order to obtain an unbiased comparison of the risks. Level of uncertainty for these estimates also should be estimated.
- It is anticipated that the risk of developing disease XYZ for the next K years (number of years depends on the length of the follow-up data) for subjects without XYZ disease and with positive test results is significantly different than for subjects with negative test results (this increase in risks should be clinically and statistically significant).

Example 3: RWD come from a “binary test” IVD, and Virtual Study is a “test with multiple categories.”

RWD

- Artificial intelligence (AI) system based on machine learning combines results from multiple IVD tests and clinical and demographic variables in a single patient-specific numeric value (e.g., a risk score) (Figure 6).
- A cutoff for the score was established in such a way that it is anticipated that risk of disease XYZ for the subjects below this cutoff will be low. It is anticipated that very high values of the score are related to very high risk of disease XYZ.
- Data of the pivotal clinical study with limited number of subjects from the target population do not have enough subjects with very high score values in order to demonstrate that risks of disease XYZ for the subjects with medium score values and for the subjects with very high score values are statistically different; therefore, the AI system was approved/cleared as a binary test (with two categories, positive and negative).
- In routine clinical practice, all subjects with AI-positive results were referred to additional testing, and finally clinical status was determined for these subjects. Subjects with AI-negative samples were not referred for determination of clinical status.

RWD (binary test)

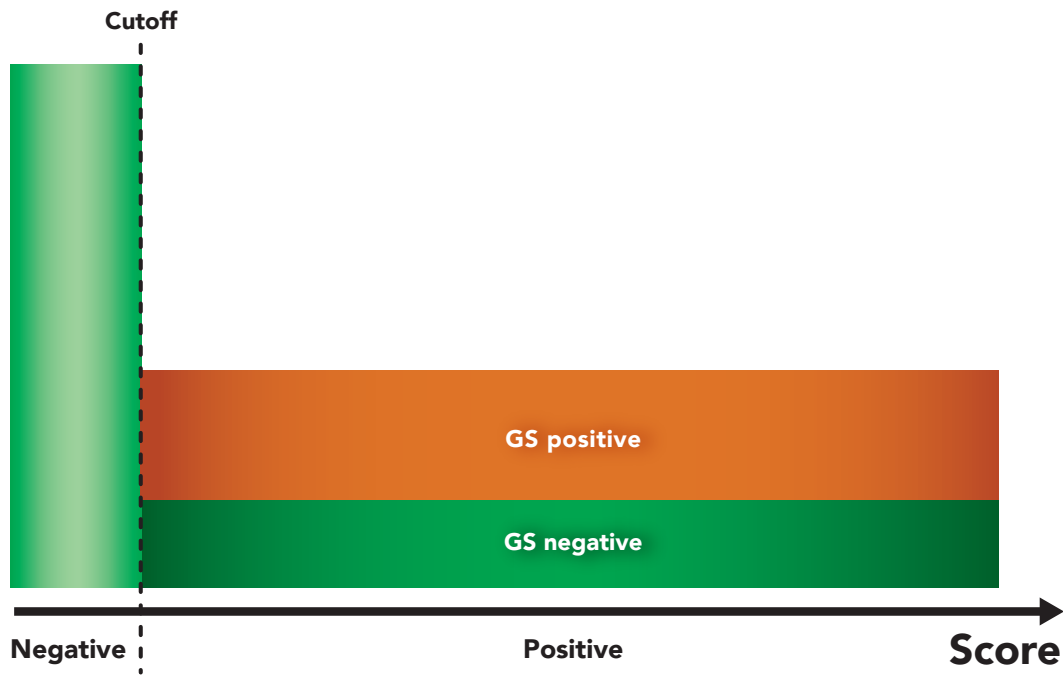


Figure 6. RWD for an AI system as a binary test. RWD are from routine clinical practice in which positive results will be referred for additional testing.

Virtual Study

One of the strengths of RWD is that these data can present a virtual study with a large number of subjects from the intended use population. All subjects with AI-positive results have results of the GS in the RWD (**Figure 7**). These subjects will be used for estimation of risks of disease XYZ for multiple categories on which category “positive” will be divided. Using a real-world database large enough to create a sufficiently powered study cohort, it can be demonstrated that risks for categories “medium positive” and “high positive” are clinically and statistically different.

Virtual study (test with multiple categories)

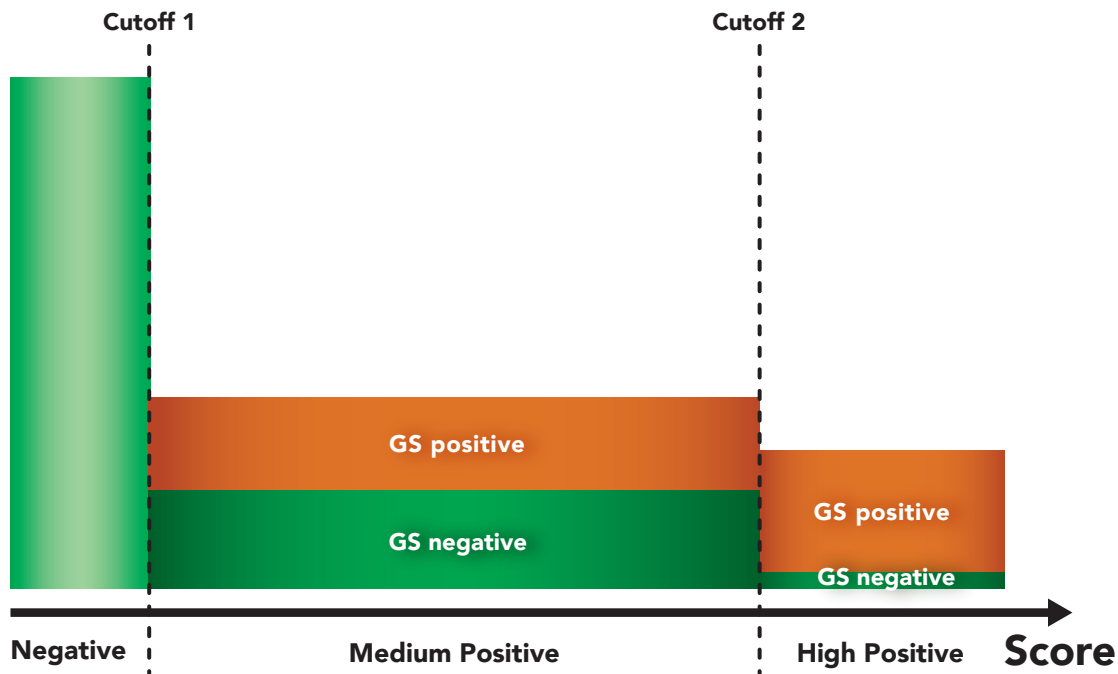


Figure 7. Virtual clinical study for an AI system as a test with three categories. In this system, the positive category is divided into two categories (medium positive and high positive).

Example 4: RWD come from “multiple individual tests,” and Virtual Study is a “new IVD device using AI/machine learning.”

RWD

RWD include routine clinical practice for patients from the target population who have multiple individual tests, and each patient has a result of the comparator method (target condition present, target condition absent) (Figure 8). These RWD can be used for developing the AI/ML system and then for evaluation of clinical performance of the AI/ML system. In this example, parts of RWD used for developing the AI/ML system are completely separate with regard to collection/testing sites or by time.^b

RWD



Figure 8. New IVD test using AI/Machine Learning. RWD are “multiple individual tests,” and the virtual study is a “new IVD device using AI/machine learning.”

In the examples above, the data can come from a variety of sources such as electronic health records (EHR) or laboratory information systems.

Virtual Study

The pivotal clinical performance study in Figure 8 is the virtual study based on real-world data. The training data set is related to the stage of development of the IVD device using AI/machine learning.

^b AI/ML is the subject of a separate MDIC framework that is still in development at the time of this publication. RWD for AI/ML will be explored in more depth in that forthcoming framework.

SECTION 6

Premarket Regulatory Assessment and Real-World Evidence

6.1 Regulatory Considerations

In order for RWE to be considered to support regulatory decisions, data should be fit for purpose. Such an assessment should include RWD that:

- Are accurate, complete, and consistent and meet key reliability and relevance criteria to inform or support a particular regulatory decision¹⁴
- Sufficiently identify the device with the level of detail necessary to address the regulatory question
- Adequately represent the intended use of the device (or proposed intended use statement, in case of expansion)
- Align with Guidance and recognized data standards acceptable to the FDA

Submitted evidence should also demonstrate that the study design used to generate RWE provides VSE to address the regulatory question and includes detailed and transparent reporting of the study design and methodology used to analyze RWD, assessment of clinically relevant differences, and reporting of relevant statistics.^{15,16}

Use of RWD also includes consideration of ethics and applicable patient privacy laws and regulations. When accessing RWD included in regulatory submissions, forethought should be given to the impact of good clinical practices, human subject protections/privacy and data access, for example, on data content, to ensure that the essential data attributes needed are retained in an unbiased manner.

Given the regulatory considerations, it is important to discuss with the FDA applicability of RWD and subsequent RWE to a specific regulatory decision early in the process. To enhance transparency and facilitate evaluation of validity, the Q-submission (Q-Sub) process offers a good opportunity for discussion of specific cases. During that process, the FDA can assess whether the individual data elements contained within an existing RWD source are sufficient to be used for the identified regulatory purpose, as well as the need for review or adjudication of specific outcomes of interest (e.g., stroke or major bleeding, at the patient level).

6.2 Clinical Considerations

It is important to understand the specific clinical question of interest and associated clinical context for the use of RWD. Key clinical considerations related to the use of RWE in an IVD regulatory submission are:

- **Relevant variables.** Sponsors should consider whether desired or necessary endpoints and other key variables relevant to the clinical question are available and adequately accessible in the RWD source (i.e., data are fit for purpose to address evidence gaps). Given these requirements, RWD may be precluded from addressing a number of regulatory evidence needs if necessary variables are not captured in routine clinical encounters or have considerable missing data.
- **Systematic biases.** The sponsor should establish valid and reliable approaches for RWD analysis and/or collection that identify and account for potential biases in the chosen clinical setting. Bias may also be addressed in appropriate study design and statistical methods/data analysis for RWE generation.

SECTION 7

Use of RWD in Postmarket Decision-Making

7.1 Postmarket Surveillance

RWD can be used for postmarket issues such as postmarket surveillance of IVDs. Ongoing surveillance may identify signals that suggest a safety and effectiveness issue. RWE may be used to refine these signals for purposes of informing appropriate corrective actions and communication.^{17,18}

For instance, leveraging surveillance networks and public health laboratories also can yield postmarket data that cannot be practically collected in a premarket clinical validation study. These networks can be used to monitor the emergence of resistant organisms as well as detect and identify biomarkers associated with disease. These networks also may provide data reflecting real-world performance of IVDs authorized for emergency use, which in turn could support marketing authorization of such IVDs.

RWD can also provide postmarket support for safety and effectiveness, where the benefit-risk associated with the IVD enables a shift of data collection from premarket to postmarket. This would be useful, for example, with low-prevalence diseases or conditions, where premarket data collection could delay an innovative IVD that could benefit patients.

SECTION 8

Strengths and Limitations of Real-World Data

8.1 General Strengths and Limitations of RWD

Understanding and addressing data strengths and limitations are foundational in deciding when and how to use RWD appropriately for IVD regulatory decision-making. The FDA RWE Guidance² relies on a multifaceted framework for suitability of RWD with emphasis on relevance and reliability (the latter being further subdivided into “data accrual” and “data assurance/quality control”). For sources of RWD, validity and reliability have emerged as common data themes, with the latter being an attempt to overlay a long-standing measure of scientific rigor and validity onto RWD.

Regardless of how data are collected, all RWD have strengths and limitations. The strengths and limitations of RWD, in general, are listed below:

Strengths

- Large, potentially heterogeneous data sets relative to data collected from clinical trials
- Potentially longitudinal and linkable data with long observation periods
- Can be used to estimate effectiveness across heterogeneous practice settings representing diverse patient populations
- Comparisons of multiple alternative diagnostics (e.g., new IVD vs. standard of care diagnostic)
- Estimates or patterns/trends of evolving optimal diagnostic including risk-benefit profile of a new diagnostic and associated long-term (and rare) clinical benefits and harms
- Information on how a test is or can be applied in clinical practice

- Data in situations where it is not possible, practical, or ethical to conduct a clinical study
- Substantiation or supplementation of data collected in more controlled settings
- Interim evidence (in the absence of relevant clinical study data) upon which preliminary decisions can be made (i.e., authorizations of emergency use of the IVD to address extraordinary unmet medical need, e.g., Zika virus IVD¹⁹)
- Postmarket data source to encourage more rapid availability of products to patients

Limitations

- Potential for systematic bias and unmeasured/residual confounding despite design and adjustments by statistical methods (compared with well-designed, executed, and analyzed clinical studies); for example, verification bias
- Laboratory results and determination of clinical status may be missing
- The identity of the manufacturer of a given test may be unknown
- Whether a test has been modified by a clinical laboratory may be unknown
- Follow-up or data linkage may be limited depending on database used (e.g., medical device registry) or due to changes in coverage (e.g., claims data)
- Lack of interoperability hinders data aggregation within and between clinical laboratories and institutions
- The routine recording of many potentially important RWD variables, including clinical laboratory results, as unstructured data limit the access and usability of RWD associated with IVDs and increase cost by necessitating curation of data into structured format to be usable
- Inability to investigate suspicious test results that may be due to lab error or unflagged interferences, for example

An applied example demonstrating limitations of RWD for IVDs is presented below (**Box 1**). Such considerations are necessary to make informed decisions around appropriate data type and source selection in addition to applying appropriate inferences to analytical results from RWD.

Common challenges surrounding RWD for IVDs include the use of unstandardized data entry and formats (despite being entered into templates) or limited visibility about the specific IVD used.

Consider a hypothetical example where Lab X uses Company ABC's BRAF genetic mutation test. Lab X can choose a variety of ways to enter that information into its system – the correct manufacturer name of the assay (ABC BRAF assay), a generic name for the assay (BRAF assay), or even the incorrect assay (selection of CDE BRAF test when the ABC BRAF test is used). Current coding often lacks the specificity to identify the actual test conducted. Additionally, in some cases, the lab may modify the test or the interpretation based on their reference population and validations.

Box 1. Example demonstrating potential RWD limitations in practice.

8.2 Systematic Bias

Systematic biases are of general concern in research, but close attention to bias is needed in the use of RWD/RWE. This document does not attempt to outline the scope of systematic biases nor to comprehensively describe how to manage bias in the generation and analysis of RWD/RWE.

Despite an investigator's concerted effort to minimize systematic biases, impacts on the observed clinical performance estimates from statistical analysis can occur. As such, it is the responsibility of the device developer to ensure that all efforts are made to minimize bias, ensuring that the observed estimates of clinical performance are as close to the true values as possible. Systematic bias can distort the meaning and impact the validity of IVD data. These biases include (but are not limited to) selection bias, incorporation bias, and verification bias. Selection bias occurs when subjects selected for the study are not representative of the overall target population (e.g., inclusion of only subjects from hospitals for evaluation of the screening assay). Incorporation bias occurs when the test under evaluation is itself incorporated in the final diagnosis and the test is evaluated versus the final diagnosis). Verification bias occurs when the execution of the comparator is influenced by the results of the test (e.g., the comparator is less frequently performed when the test result is negative). Severe verification bias occurs when all subjects from some subset (e.g., subjects with negative test results do not have results of the comparator according to routine clinical practice).

8.3 Missing Data

Regarding missing data, sponsors may want to address implications of how missingness may influence (and bias) study results. This is largely based on the type of missingness present. In its most extreme form, a variable may be missing completely (e.g., laboratory results in administrative claims databases). However, in those data sources selected as fit for purpose, the issue of missing data is more commonly that of a missing value of one or more variables across different observations. How missing data will be handled and inferences interpreted is often a function of the model being used. For example, in RWD for developing the AI/ML system where multiple laboratory tests are used, missingness across variables can compound and impact the absolute number of patients included in the analysis despite the degree of missingness being relatively small for a given variable.

SECTION 9

Real-World Data Relevance

Use of RWD for regulatory decision-making includes assessment of data relevance and reliability against its source or a set of standards (e.g., documented standardization methods, comprehensiveness, validation, and interpretation of perspective from patient to provider). Considerations²⁰ around RWD for regulatory decision-making include (i) data relevance, (ii) reliability and validity, (iii) linkages, and (iv) eligibility. Relevance speaks to the appropriate selection of RWD to answer in whole or in part the regulatory question for a given product. Reliability, on the other hand, includes data accrual and data quality control (data assurance).

9.1 Assessing Data Relevance

Selected RWD should be relevant to, and representative of, clinical practice and the healthcare system in the U.S., where the IVD will be deployed. Thus, careful selection of U.S. and outside of U.S. data should be made, as inferences of results and generalizability to patient populations to whom the diagnostic will be applied need to be demonstrated. Early interaction with the FDA may be valuable. Pertinent issues include:

- The rationale for data source selection according to evidence needs and study purpose,² often driven by the IVD's intended use statement
- Information on the healthcare system (if potentially different from the U.S. healthcare landscape for whom the IVD is intended), including method(s) of diagnosis and preferred treatment patterns for the disease(s) of interest, and degree to which this information is collected in the selected data source(s)
- Consideration of population and demographic characteristics (e.g., race, ethnicity, age, and disease prevalence)
- Description of IVD utilization patterns and, potentially, treatment patterns (if relevant to the given diagnostic)
- Information of market availability of the IVD, which may include a predicate device
- An explanation of how these factors might influence generalizability of the study results to the target U.S. population

Ascertainment of such information may be challenging in certain settings and for certain conditions, and justification of the population to capture the relevant data elements should be documented. The use of a flow diagram may aid in visually demonstrating attrition^{21,22} and is an easily referenced visible record of study process.

The background is a solid teal color. In the upper left corner, two thin white lines extend diagonally towards the right. Each line ends with a small white dot. The lines are parallel and slightly curved. The overall design is minimalist and modern.

Appendices

Appendices

10.1 Appendix A: Examples of IVD Regulatory Assessment Using Real-World Evidence

To date, few sponsors have taken advantage of RWE to support regulatory decisions for their IVD products. However, several examples are presented below and may best reflect the considerations of RWD and RWE included in this Framework.

Example: Detecting Genetic Changes Associated with Cystic Fibrosis (CF)

The November 19, 2013, marketing authorization of the Illumina MiSeqDx CF products used RWE to support clinical validation. The device is used to detect DNA changes in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which can result in cystic fibrosis (CF). Data about which DNA changes are associated with symptoms of CF were obtained from the CFTR2 database.²³ This multi-site, multinational database included genetic information collected in routine clinical practice from patients diagnosed with CF. Recent efforts focused on ascertaining which mutations were disease liabilities through the Clinical and Functional Translation in the CFTR project.²⁴

Illumina submitted evidence of variants detected from dried blood spot specimens collected through routine newborn CF screening and included in the CFTR2 database to estimate the clinical sensitivity and specificity of the IVD. They also included comparisons of the sequence results to Human Genome Build 19, a reference representation of the human genome. Instrument and reagent system performance were also evaluated against a publicly available quality-weighted human reference genome created through a collaboration between the FDA and the National Institute of Standards and Technology (NIST).

Example: Memorial Sloan-Kettering (MSK) Cancer Center MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)

Sponsor-submitted RWE played a role in the November 15, 2015, marketing authorization of the MSK-IMPACT, a next generation sequencing (NGS)-based tumor profiling test through the De Novo classification process.²⁵ In contrast to the distributed product described above for CF, the MSK-IMPACT assay is a single-site assay. The assay is an IVD that uses targeted NGS of tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi-gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability.

Companion diagnostic IVDs, necessary for the safe and effective use of a specific drug product, typically require a premarket approval (PMA). To allow for a least-burdensome approach for tumor profiling, the FDA allowed an intended use that limited the IVD for use by qualified healthcare professionals in accordance with professional guidelines, with the labeling clearly indicating that the IVD is not conclusive or prescriptive for labeled use of any specific therapeutic product. As part of this marketing authorization, the FDA published a groundbreaking pathway, in the form of an FDA Fact Sheet: CDRH'S Approach to Tumor Profiling Next Generation Sequencing Tests,²⁶ for use of accepted clinical evidence.

MSK-IMPACT used a clinical evidence curation resource (OncoKB) to facilitate the clinical interpretation of detected mutations. OncoKB is a knowledge base that includes biologic, clinical, and therapeutic information curated from multiple information resources including professional guidelines and recommendations, therapeutic labeling, disease-specific expert and advocacy group recommendations, and medical literature. OncoKB information is publicly available through an interactive website. Classification criteria were developed by MSK to communicate the level of clinical evidence available for individual mutations in the test report. The mutations were reported under



two categories (i.e., cancer mutations panel with evidence of clinical significance and cancer mutations panel with potential clinical significance) based on prespecified classification criteria. OncoKB undergoes periodic updates through the review of new information by a panel of experts.

10.2 Appendix B: Glossary

To date, few sponsors have taken advantage of RWE to support regulatory decisions for their IVD products. However, several examples are presented below and may best reflect the considerations of RWD and RWE included in this Framework.

<p>ADMINISTRATIVE CLAIMS DATA</p>	<p>Data arising from a person’s use of the healthcare system and reimbursement of healthcare providers for that care.</p> <p>Reference: FDA (2013); Guidance for Industry and FDA Staff Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.</p>
<p>BIAS</p>	<p>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.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
<p>DATA ELEMENT</p>	<p>A single observation associated with a subject in a clinical study. Examples include birth date, white blood cell count, and other clinical observations made and documented during a study.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
<p>ELECTRONIC HEALTH RECORD (EHR)</p>	<p>An individual patient record contained within the EHR system. A typical individual EHR may include a patient’s medical history, diagnoses, treatment plans, immunization dates, allergies, radiology images, pharmacy records, and laboratory and test results. This Guidance uses a broad definition to be inclusive of many different types of EHRs and may not be consistent with the definition published in other Guidance documents.</p> <p>Reference: FDA (2018); Use of Electronic Health Record Data in Clinical Investigations, Guidance for Industry, July 2018.</p>

<p>ELECTRONIC HEALTH RECORD (EHR) SYSTEMS</p>	<p>Electronic platforms that contain individual health records for patients. EHR systems are generally maintained by healthcare providers, healthcare organizations, and healthcare institutions and are used to deliver care. EHR systems can be used to integrate real-time electronic healthcare information from medical devices and multiple healthcare providers involved in the care of patients.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
<p>HARMONIZATION</p>	<p>Data harmonization refers to all efforts to combine data from different sources and provide users with a comparable view of data from different studies.</p> <p>Reference: Doiron, D., Burton, P., Marcon, Y. et al. Data harmonization and federated analysis of population-based studies: the BioSHaRE project. <i>Emerg Themes Epidemiol.</i> 2013;10(1).</p>
<p>HETEROGENEITY</p>	<p>The variability between patients included in an analysis, due to differences in characteristics. Such variability may lead to differences in the observed clinical performance characteristics as clinical sensitivity and clinical specificity.</p>
<p>INTEROPERABILITY</p>	<p>The ability of two or more products, technologies, or systems to exchange information and to use the information that has been exchanged without special effort on the part of the user.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
<p>MEDICAL DEVICE REGISTRY</p>	<p>An 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.</p> <p>References: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
<p>OBSERVATIONAL STUDY</p>	<p>A study that does not involve any intervention (experimental or otherwise) on the part of the investigator.</p> <p>References: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>



POSTMARKET	The period after launch of a specific medical device product in the market.
POSTMARKET SURVEILLANCE	<p>The active, systematic, scientifically valid collection, analysis, and interpretation of data or other information about a marketed device.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
REAL-WORLD DATA (RWD)	<p>Data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
REAL-WORLD EVIDENCE (RWE)	<p>The clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.</p> <p>Reference: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>
REGISTRY	<p>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.</p> <p>References: FDA (2017); Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Final Guidance for Industry and Food and Drug Administration Staff, August 31, 2017.</p>

<p>SAFETY AND EFFECTIVENESS</p>	<p>1) Safety: There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.</p> <p>2) Effectiveness: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.</p> <p>References: Code of Federal Regulations: 21 CFR 860.7 (d)(1). https://www.ecfr.gov/cgi-bin/text-idx?SID=2ab340080e76eafcb089793d004bb949&mc=true&node=pt21.8.860&rgn=div5#se21.8.860_17</p> <p>Code of Federal Regulations: 21 CFR 860.7 (e)(1). https://www.ecfr.gov/cgi-bin/text-idx?SID=2ab340080e76eafcb089793d004bb949&mc=true&node=pt21.8.860&rgn=div5#se21.8.860_17</p>
<p>SOURCE DATA</p>	<p>All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).</p>
<p>VIRTUAL STUDY</p>	<p>A study based on RWD that imitates (simulates) a clinical performance study in the best possible way with regard to an intended use population, intended type of specimens, intended operators, and an evaluation of measures of the clinical performance (e.g., sensitivity and specificity for binary qualitative tests).</p>



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SECTION 11

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