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ADMINISTRATION

FRAMEWORK FOR FDA'S
**REAL-WORLD
EVIDENCE
PROGRAM**

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Framework for FDA's Real-World Evidence Program

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Introduction

The 21st Century Cures Act (Cures Act),¹ signed into law on December 13, 2016, is designed to accelerate medical product development and bring new innovations and advances faster and more efficiently to the patients who need them. Among other provisions, the Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Pursuant to this section, the Food and Drug Administration (FDA) has created a framework for evaluating the potential use of real-world evidence (RWE) to help support the approval of a new indication for a drug² already approved under section 505(c) of the FD&C Act or to help support or satisfy drug postapproval study requirements.³ In addition to drug and biological products approved under section 505(c), this framework is also intended for application to biological products licensed under the Public Health Service Act.⁴ The framework does not cover medical devices.⁴

FDA's RWE Program will be multifaceted. It will involve demonstration projects, stakeholder engagement, internal processes to bring senior leadership input into the evaluation of RWE and promote shared learning and consistency in applying the framework, and guidance documents to assist developers interested in using real-world data (RWD) to develop RWE to support Agency regulatory decisions. This document outlines the framework FDA plans to use to implement its RWE Program.

¹ [Public Law 114-255](#).

² For purposes this framework, unless otherwise noted, the term drug refers both to a drug approved under section 505(c) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and to biological products licensed under section 351 of the [Public Health Service Act \(PHS Act\) 42 USC 262](#).

³ In this document, when we refer to the use of RWE to support a regulatory decision, we mean that the evidence provides support for or helps provide support for the regulatory decision.

⁴ FDA issued the guidance [Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices](#) on August 31, 2017.



Definitions of Real-World Data and Real-World Evidence

Section 505F(b) of the FD&C Act defines RWE as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials” ([21 U.S.C. 355g\(b\)](#)).⁵ In developing its RWE program, FDA believes it is helpful to distinguish between the sources of RWD and the evidence derived from that data. Evaluating RWE in the context of regulatory decision-making depends not only on the evaluation of the methodologies used to generate the evidence but also on the reliability and relevance of the underlying RWD; these constructs may raise different types of considerations. For the purposes of this framework, FDA defines RWD and RWE as follows:

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

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

⁵ The definition of RWE provided by section 3022 of the Cures Act was subsequently revised by a technical amendment in Section 901 of the FDA Reauthorization Act of 2017 (Public law 115-52).

Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, administrative and medical claims databases) can be used for data collection and, in certain cases, to develop analysis infrastructure to support many types of study designs to develop RWE, including, but not limited to, randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies (prospective or retrospective).⁶

Clinical Trials and Observational Studies Covered by the RWE Program

It is important to distinguish among the trial designs and studies that will be covered by the RWE Program. Under FDA's RWE Program, evidence from traditional clinical trials will not be considered RWE. However, various hybrid or pragmatic trial designs and observational studies could generate RWE. FDA's RWE Program will cover clinical trials that generate RWE in some capacity (i.e., sources other than traditional clinical trials) and observational studies.

Clinical Trials. For the purposes of this framework, a *clinical trial* is defined as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁷

Although there is no single definition of a traditional clinical trial — and indeed trials vary considerably in design and conduct — for the purposes of this framework, FDA generally considers a traditional clinical trial to be one that is usually supported by a research infrastructure that is largely separate from routine clinical practice and is designed to control variability and maximize data quality. A traditional clinical trial is more likely to have restrictive eligibility criteria that are designed to ensure that the participants have the disease of interest or have characteristics in which detection of a drug effect (if one is in fact present) is more

⁶ Randomized and observational study designs are discussed further in this framework. For a discussion about large simple trials, see Peto et al. 1995 and Eapen et al. 2014. For a discussion about pragmatic clinical trials, see Ford and Norrie 2016.

⁷ In this document and for purposes of the RWE program, we also refer to a *clinical trial* as a type of *clinical study*. This should not be read to suggest that FDA considers clinical trials to be studies under section 505(o), which authorizes FDA to require postapproval clinical trials and studies under specific conditions.

likely than it would be if the population were less precisely defined. Traditional clinical trials are usually randomized, double-blind trials in which both the investigator and patient are unaware of which treatment is being administered. These trials typically use separate procedures and/or identified research personnel, or both, to collect specified data using standardized procedures and detailed *case report forms* (CRF) that are separate from routine medical records, although some data (e.g., locally obtained lab data) may be transcribed from those records into the CRF. Personnel follow specified protocol directives to conduct scheduled monitoring and encourage precise adherence to study procedures.

Some clinical trials may use hybrid design. For example, certain elements of a clinical trial could rely on the collection and analysis of RWD extracted from medical claims, EHRs, or laboratory and pharmacy databases. Researchers could collect other data specifically for the trial, such as results of exercise stress tests or radiographic analyses, using methods typical of a traditional clinical trial. A hybrid trial could use RWD for one clinical outcome (e.g., hospitalization, death), while other elements were more traditional (e.g., specified entry criteria, monitoring and collection of additional study endpoints by dedicated study personnel). FDA will consider these hybrid trial designs to have the potential to generate RWE. Clinical trial designs can also include some elements that more closely resemble routine clinical practice, which are sometimes described as “pragmatic” elements. These pragmatic clinical trials often rely on RWD and have the potential to generate RWE.

Observational Studies. For purposes of this framework, *observational studies* are non-interventional clinical study designs that are not considered clinical trials. FDA considers a *retrospective observational study* to be one in which the study identifies 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 designed. In a *prospective observational study*, the population of interest is identified at the start of the study, and exposure/treatment and outcome data are collected from that point forward. The start of the study is defined as the time at which the research protocol for the specific study question is initiated. Observational clinical studies might be another way to generate RWE that is relevant to effectiveness determinations. Therefore, the RWE Program will also consider the evaluation of observational clinical studies using RWD to support product effectiveness determinations.

Scope of RWE Program Under 21st Century Cures Act

Under the Cures Act, FDA's RWE Program must evaluate the potential use of RWD to generate RWE of product effectiveness to help support approval of new indications for drugs approved under FD&C Act Section 505(c) or to help to support or satisfy postapproval study requirements. FDA's RWE Program will also apply to biological products licensed under section 351 of the Public Health Service Act.

RWD can also be used to improve the efficiency of clinical trials, even if not used to generate RWE regarding product effectiveness. For example, RWD can help with:

- Generating hypotheses for testing in randomized controlled trials
- Identifying drug development tools (including biomarker identification)
- Assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population, both within a geographical area or at a particular trial site
- Informing prior probability distributions in Bayesian statistical models
- Identifying prognostic indicators or patient baseline characteristics for enrichment or stratification
- Assembling geographically distributed research cohorts (e.g., in drug development for rare diseases or targeted therapeutics)

Because the use of RWD to improve efficiencies of drug development programs that rely primarily on traditional clinical trials is already well established and generally encouraged by FDA, that approach will not be the focus of this framework. The framework covers the use of RWE in the other areas described in this document.

“As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information.”

Scott Gottlieb, FDA Commissioner
National Academies of Science, Engineering, and Medicine,
 Examining the Impact of RWE on Medical Product Development,
 September 19, 2017

Current Use of RWD for Evidence Generation

Generating Evidence Regarding Safety and Effectiveness

FDA has a long history of using RWE to monitor and evaluate the safety of drug products after they are approved (postmarket). FDA's primary source for executing pharmacoepidemiologic queries and studies is electronic health data (medical claims and pharmacy dispensing data) in the *Sentinel System*, which as of August 2018 has data on more than 100 million individuals within a network of 18 data partners and collaborating institutions.⁸ Multiple data sources are often queried to conduct an analysis of how drugs and biologics are used and to evaluate safety issues. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) perform safety monitoring studies through pharmacoepidemiologic research projects under the [Sentinel Initiative](#) (Ball et al. 2016).

Based on the identification of a safety concern, FDA may begin planning for a study using the Sentinel System even before a drug is approved. FDA first designs a query that can be executed by the Sentinel System data partners to provide information on the safety question. In addition, FDA designs studies to examine safety questions identified after a drug is approved. For example, FDA used the Sentinel System to evaluate the risk of stroke after using antipsychotics (Taylor 2017), the risk of seizures after using ranolazine (Eworuke 2017), and the risk of venous thromboembolism after an extended or continuous cycle of oral contraceptives (Meony 2017).

CDER and CBER also perform pharmacoepidemiologic studies in collaboration with other Federal partners including the Centers for Medicare & Medicaid Services (CMS) and the Veterans Health Administration. In addition, CDER uses the [Clinical Practice Research Datalink](#), which captures United Kingdom longitudinal patient-level EHR data. CDER uses RWD from the Centers for Disease Control and Prevention National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, an active surveillance system operating in approximately 60 hospital emergency departments across the United States to specifically evaluate drug abuse, misuse, and the potential for self-harm.

⁸ A list of collaborating institutions is available at <https://www.sentinelinitiative.org/collaborators>.

In addition, CBER has created focused surveillance efforts within the Sentinel System for vaccine safety, using the Post-Licensure Market Rapid Immunization Safety Monitoring (PRISM) system, and for blood components and blood derived products with the Blood Surveillance Continuous Active Surveillance Network (BloodSCAN). In September 2017, CBER launched the Sentinel Biologics Effectiveness and Safety (BEST) system, an expansion of the Sentinel Initiative and other evidence generation capabilities that adds a number of new data sources, including EHR and *medical claims data*, new analytic tools, and new collaborating institutions.

However, the use of RWE to support effectiveness determinations is much more limited. For example, CBER has used CMS data to evaluate the comparative effectiveness of preventative vaccines, including standard-dose and high-dose (Izurieta et al. 2015); egg-based, cell-based, and adjuvanted influenza vaccines (FDA et al. 2018); and the effectiveness of a herpes zoster vaccine (Izurieta et al. 2017).

Supporting FDA's Regulatory Decisions of Effectiveness

In limited instances, FDA has accepted RWE to support **drug product** approvals, primarily in the setting of oncology and rare diseases. When approval is based on a single-arm interventional trial — often when using a parallel assignment control arm is unethical or not feasible and usually when the effect size is expected to be large, based on preliminary data — the supportive RWE has consisted of data on historical response rates drawn from chart reviews, expanded access, and other practice settings.

Blincyto (blinatumomab) was initially approved under accelerated approval for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia, based on evidence of complete remission (CR) and duration of CR from a single-arm trial, the response rate of which was compared to historical data from 694 comparable patients extracted from over 2,000 patient records from European Union and U.S. clinical study and treatment sites (Przepiorka et al. 2015). Further study in a randomized controlled trial was required by FDA to verify the clinical benefit (Tower study [NCT02013167](#)).

Trials Generating RWE

Randomized trial using RWD to assess dose response: ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness; start date April 2016) ([NCT02697916](#)).

This pragmatic clinical trial compares two commonly used aspirin doses, 81 mg and 325 mg, by randomizing 20,000 patients with a history of myocardial infarction or known atherosclerotic cardiovascular heart disease to one of the two doses. The trial uses electronic algorithms to identify potential participants from the National Patient-Centered Clinical Research Network (PCORnet) health system partners. The trial is integrated into routine clinical care with minimal inclusion/exclusion criteria and no treatment protocol requirement beyond the assignment to one of the two doses of aspirin. The trial is using EHRs and claims data (through PCORnet) to capture primary endpoints such as death, hospitalization for non-fatal myocardial infarction or non-fatal stroke, and secondary endpoints such as coronary revascularization procedures, hospitalization for serious bleeding, and other patient-reported outcomes (Hernandez et al. 2015).

Randomized trial using an established registry: VALIDATE-SWEDEHEART (The Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry Trial; December 2014–May 2017) ([NCT02311231](#)). This trial was a registry-based, multicenter trial in which patients were randomized to bivalirudin or heparin during percutaneous coronary intervention. The composite endpoint was myocardial infarction, all-cause mortality, and major bleeding at 6 months. A national population-based Swedish registry platform was used for continuous enrollment (all patients at participating centers were evaluated for enrollment), randomization, data collection (including baseline demographic data, procedural data, and clinical outcomes), and follow up (Fröbert et al. 2013).

Trial Designs Using RWD to Generate Evidence

Randomized Controlled Trials Integrated into Health Care Systems

The integration of clinical trials into health care systems and capturing outcomes from clinical practice is not new. For example, in the late 1980s, researchers in Italy (Maggiono et al. 1990) conducted a randomized clinical trial at the site of routine clinical care by randomizing 11,712 patients with acute myocardial infarction to receive either standard care or standard care and 1.5 million units of streptokinase intravenously. A stated objective of the trial was to eliminate the divide between clinical research and clinical practice (Rovelli et al. 1987). Nearly all cardiac care units in Italy participated in the trial, and outcomes included in-hospital mortality and mortality at 6 and 12 months.

As previously noted, clinical trials can be integrated into the health care system and can include some pragmatic elements. Trial integration should facilitate collection of outcomes and serious adverse events using RWD. The box **Trials Generating RWE** provides examples of trials using RWD to generate evidence about the potential benefits or risks of a drug. These trials share certain characteristics, including use of outcomes when there may be less diagnostic variability, which therefore may be well captured in RWD sources. In addition, the lack of blinding is less likely to influence outcomes such as myocardial infarction or stroke.

Observational Studies Using RWD to Generate RWE

Observational studies have been used to support regulatory safety decisions; however, treatment assignment based upon physician judgment, rather than random assignment, creates a challenge for establishing causal inference that must be addressed to support the acceptability of observational studies for effectiveness decisions. Randomization is used to prevent bias in allocation of the intervention by creating study groups balanced for risk factors for the targeted outcome and has been considered a critical element in establishing a causal relationship between medication use and health care outcomes.

Although observational studies may provide credible evidence, there is a stronger scientific justification for deriving evidence of a drug effect from randomized controlled trials as compared to observational studies. Despite literature citing examples where observational and

randomized trials have reached similar conclusions about treatment effect (Benson and Hartz 2000; Anglemyer et al. 2014), there are also examples when effects identified in observational studies could not be reproduced in randomized trials or when the effect sizes differed in direction or magnitude (e.g., Cooper et al. 2014; Hemkens et al. 2016; Guadino et al. 2018).

FDA is aware of recent efforts to use rigorous design and statistical methods to replicate randomized trial results with observational studies and to derive general rules that might increase the chance of obtaining valid results using RWD in observational study designs (Franklin and Schneeweiss 2017). As previously noted, although some examples show concordance between randomized trials and observational studies, other examples show divergence. As recognized by the authors of a recent observational study that was designed to replicate the findings of a regulatory drug trial (Fralick et al. 2017), retrospective reviews of the literature comparing randomized clinical trial results to observational studies “provide single summarizations of the differences between these two approaches but provide few insights on the validity of individual real-world data analyses.” The authors further suggested that “to establish a meaningful baseline, the FDA will need many sets of randomized clinical trials with prospectively designed, nonrandomized analyses to match the populations included in randomized clinical trials across a range of clinical questions, each investigated with a set of designs and methods following rigorous epidemiologic principles.”

As part of its RWE Program, FDA will evaluate the potential role of observational studies in contributing to evidence of drug product effectiveness. Efforts to replicate the results of randomized controlled trials using more rigorously designed observational studies may provide insight into the opportunities and limitations of using these designs in regulatory decisions.

Framework for Evaluating RWD/ RWE for Use in Regulatory Decisions

Using Trials or Studies with RWD/RWE for Effectiveness Decisions

As previously noted, there is considerable interest in using RWD to generate RWE to support regulatory decisions about the effectiveness of drug products. FDA has used RWD primarily in its evaluation of safety and only in limited circumstances to inform decisions about effectiveness. FDA's RWE Program will therefore focus on exploring the potential of RWD/RWE to support regulatory decisions about product effectiveness. Specifically, FDA's RWE Program will evaluate the potential use of RWE to support changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration; adding a new population; or adding comparative effectiveness or safety information.

The framework will include consideration of the following:

1. Whether the RWD are fit for use
2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

FDA intends to use this three-part approach to evaluate individual supplemental applications, as appropriate, and more generally to guide FDA's RWE Program. The RWE Program will involve the establishment of demonstration projects, engagement with stakeholders, the use of internal processes that bring senior leadership input into the evaluation of RWE and promote shared learning and consistency in applying the framework, and the development of guidance documents to assist sponsors interested in using RWE to support their work.

Additionally, to efficiently process RWD and submit it for evaluation to FDA, appropriate data standards are necessary. A data standard is a set of rules about how a particular type of data should be structured, defined, formatted, or exchanged between computer systems. Data standards make submissions predictable and consistent and have a form

"FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."

Janet Woodcock, M.D., Director, CDER

that an information technology system or a scientific tool can use. To work with RWD across multiple sources, data may need to be put into a common format, sometimes referred to as a common data model (CDM), with common representation (terminologies, vocabularies, coding schemes). FDA recognizes the importance of developing data standards to maximize the utility of RWD and is working on identifying relevant standards and methodologies for collection and analysis of RWD. FDA has already been active in developing data standards for regulatory use and will continue to expand its work in this area. FDA will consider data standards along with the other critical aspects of the RWE Program.

Assessing Fitness of RWD for Use in Regulatory Decisions

Assessing Data Reliability (Data Accrual and Data Assurance) and Relevance

The strength of RWE submitted in support of a regulatory decision depends on the clinical study methodology and the reliability (data accrual and data quality control (data assurance)) and relevance of the underlying data. In general, FDA does not endorse one type of RWD over another. Data should be selected based on their suitability to address specific regulatory questions. For the purposes of evaluating drug safety, for example, FDA has already outlined its perspective on using RWD available in electronic health care data systems for safety studies in its guidance for industry and staff [Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data](#) (Pharmacoepidemiologic Guidance). The Pharmacoepidemiologic Guidance includes recommendations for evaluating the data sources used in pharmacoepidemiologic safety studies.

FDA has gained considerable experience assessing electronic health care data (e.g., EHRs, medical claims data, registries) through experience with the Sentinel System and other data systems. To assess the RWD used to generate RWE in the Sentinel System, FDA considers data reliability and relevance. Reliability includes data accrual and data quality control (data assurance). For medical claims data, this would include the assessment that the International Classification of Diseases (ICD) codes (e.g., ICD-ver.10-Clinical modification (CM)), which describe the medical diagnosis for which a claim is submitted, are present and in the appropriate format for use with the Sentinel System CDM and analysis tools. For EHRs, since laboratory test results obtained during routine care are not uniformly coded or documented in



a standardized manner between organizations or within organizations over time, the reliability assessment includes checking the laboratory data for completeness, consistency, and trends over time, including the use of reporting standards such as the Logical Observation Identifiers, Names, and Codes (LOINC) system.

While the reliability assessments consider whether the codes or combinations of codes adequately represent the underlying medical concepts they are intended to represent, the relevance assessment considers whether the data are fit for purpose and include an assessment of whether the data capture relevant data on exposure, outcomes, and covariates. In the context of the Sentinel System, the relevance assessment also considers whether the CDM contains the critical data elements and whether available analytic tools are sufficient to address each question of interest.

FDA intends to adapt this approach to assess sources of RWD used to generate RWE of drug product effectiveness, recognizing that the specific elements to consider will likely differ by RWD type and the type of research for which the data are intended. For example, U.S.

government agencies, health care insurers, and researchers have substantial experience checking data quality, validating the data, and using medical claims data for public health and research purposes (mostly in observational studies), and there is a good understanding of the strengths and limitations of using medical claims data as RWD. On the other hand, EHR data, which should provide more detailed data on the patient beyond information contained within medical claims data (i.e., diagnosis codes and prescriptions or other procedures), do not usually show standardized data in structured fields that can be readily extracted and compared across systems. In addition, certain covariates



(e.g., obesity, smoking, alcohol use) and outcomes (e.g., mortality, symptomatic changes) may not be consistently captured in EHRs or medical claims data. It will be important to examine data relevance to determine whether the full range of outcomes that could be used for study endpoints (e.g., disease exacerbations, hospitalization for specialized conditions, other kinds of disease outcomes) are captured.

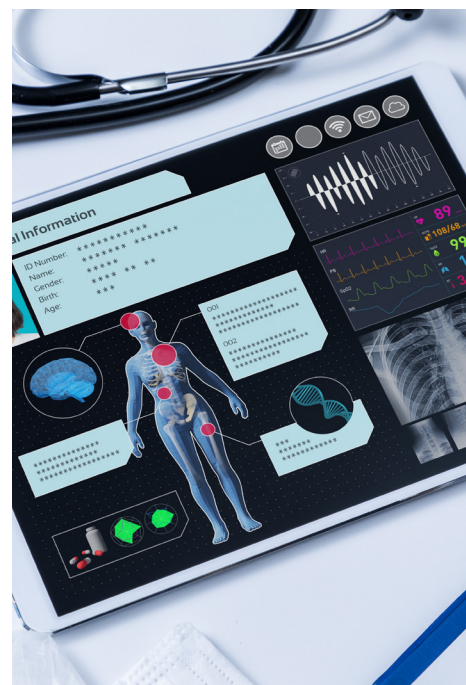
Data from other countries can be another valuable source of RWD, but their fitness for use in FDA regulatory decision-making could be limited by important differences in health care systems. Using data from other countries might require analyses that consider the differences in medical practice, health care delivery, and data reliability and relevance compared to the United States. FDA's Pharmacoeconomic Guidance provides considerations for using international electronic health care data in safety studies. FDA's RWE Program will explore

those considerations when using international electronic health care data to generate RWE about drug product effectiveness for regulatory decision-making.

Patient registries are another source of RWD that could be used to generate RWE. A patient registry is 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 (Gliklich et al. 2014). Registries are generally defined either by diagnosis of a disease (disease registry) or usage of a drug, device, or other treatment (exposure registry) (CTTI 2017). Their fitness for use in generating RWE requires sufficient processes, such as those to gather follow-up information when needed, to ensure data quality, and to minimize missing or incomplete data.

Although different RWD sources will have different strengths and limitations, the selection of appropriate RWD sources should be based on the regulatory question of interest and should be collected and maintained in a way that provides an appropriate level of reliability.

Program Item. Building on the Pharmacoepidemiologic Guidance, FDA plans to issue guidance on how to assess the reliability and relevance of RWD from medical claims and EHRs used to generate RWE regarding drug product effectiveness. FDA will also examine how to assess the reliability and relevance of registry data and international electronic health care data.



Addressing Gaps in RWD Sources

EHRs and medical claims data may not capture all data elements needed to answer the question of interest. We expect that these sources will generally record major events like hospitalization, but other changes in medical status (e.g., worsening of depression or anxiety, increased joint pain, changes in severity of a dermatologic condition, worsening asthma) may not be reliably and consistently documented in the EHR, if at all. Even when captured, the way the data elements are captured in the EHR may limit their accessibility. For example, a patient's symptoms may be recorded in unstructured data in the physician's note without the use of standardized language or a standard symptom scale. Data on changes in the severity of chronic conditions over time are not likely readily available in medical claims data.

More effective development and use of RWE will require that information within EHRs be more accessible and connected, and tools must be developed to facilitate searching such records. As described previously, both EHRs and medical claims data may not capture patient experience, unless the patient's experience is recorded as a clinical event by health care providers (e.g., hospitalization or referral to another provider). *Patient reported outcomes*,⁹ changes in responses to medication, or non-serious adverse events might not be reported to caregivers or at health care visits. Even if the data are captured in the EHR, different health care systems may use EHRs in different formats, making it difficult to collect the same data across the varying records. Moreover, because health care systems often are not interoperable, it is difficult to integrate their data systems. This makes it especially difficult to capture data as patients move between providers or seek care in other facilities. Medical claims data may be able to follow an individual over time and across sites of care, but may be limited if individuals change insurers. Medical claims data also often lack the clinical granularity needed to answer certain questions.

FDA will explore strategies for filling gaps in data that may be difficult to obtain from currently used EHRs and medical claims data, including exploring the use of mobile technologies, electronic patient reported outcome tools, wearables, and biosensors.

Another important challenge is the difficulty in connecting or integrating various data sources contributing information about an individual patient. Unlike in some countries, patients in the United States do not have a single identification number that is used across private health care systems, similar to the social security number that are used by the U.S. government in the Medicare coverage system. Therefore, methods will need to be developed to address duplication of patient information in different data sources and to enable linking data about a single patient across data sources while protecting patient privacy. In health care settings in which a significant number of individuals move between health care plans and insurers, it may be difficult to capture outcomes that occur over years rather than months. FDA's RWE Program provides an opportunity to address these challenges and improve the reliability and relevance of RWD sources.

Program Item. FDA will review and, where applicable, publish guidance on potential gaps in RWD sources and strategies to address them.

⁹ See FDA guidance [Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims](#).

Potential for Study Designs Using RWD to Support Effectiveness

Randomized Designs Using RWD

RWD can be used in a variety of ways and be included in different study designs. As previously noted, FDA sees promise in the opportunities created by pragmatic clinical trials, including broader inclusion/exclusion criteria and streamlined data collection.

Depending on the nature of the disease, the patient population, interventions, and other factors relevant to the trial, it may be possible to design hybrid trials that include both traditional and pragmatic clinical trial elements. FDA, therefore, will evaluate the strengths and limitations of pragmatic approaches using RWD, considering some important factors:

- What types of interventions and therapeutic areas might be well-suited to routine clinical care settings?
- What is the quality of data that can be captured in these settings?
- How many patients can be accessed (particularly when outcomes are rare)?
- What are the variations inherent in clinical practice?

When blinding of treatment is infeasible, FDA will seek to identify situations when bias resulting from lack of blinding can potentially be controlled using outcomes that are less likely to be influenced by knowledge of treatment assignment, such as clinically objective outcomes (e.g., stroke, tumor size). However, even when using objective assessments, approaches to ensure consistency in outcome ascertainment and reporting will be important. Finally, FDA will explore the feasibility of different randomization approaches in pragmatic clinical trials, including cluster randomization by institution or practice.

Program Item. FDA's RWE Program will develop guidance on considerations for designing clinical trials that include pragmatic design elements and that generate evidence of effectiveness for regulatory decisions. FDA will explore pragmatic approaches to each stage of a clinical trial, including recruitment and enrollment of patients, strategies for facilitating interventions, and approaches to assessing outcomes.

Non-randomized, Single Arm Trials with External RWD Control

External controls (e.g., historical controls) are a possible type of control arm in an adequate and well-controlled study.¹⁰ Typically, the external control arm uses data from past traditional clinical trials, but in some cases, RWD have been used as the basis for external controls. Using external controls has limitations, including difficulties in reliably selecting a comparable population because of potential changes in medical practice, lack of standardized diagnostic criteria or equivalent outcome measures, and variability in follow-up procedures. Collection of RWD on patients currently receiving other treatments, together with statistical methods, such as propensity scoring, could improve the quality of the external control data that are used when randomization may not be feasible or ethical, provided there is adequate detail to capture relevant covariates.

Program Item. Guidance on the use of RWD to generate external control arms is also being considered.

Observational Studies

Pharmacoepidemiology studies are observational studies that examine how drugs are used and their effects in populations. Broadly speaking, pharmacoepidemiology focuses on selecting the appropriate data, design, and analysis to obtain a valid and unbiased answer to the question of interest using RWD.

FDA has substantial experience evaluating and providing guidance on pharmacoepidemiology studies that use RWD in the context of safety. As previously stated, for the purposes of evaluating drug safety, FDA has already outlined its perspective on using RWD available in electronic health care data systems (medical claims and EHRs) for safety studies in the Pharmacoepidemiologic Guidance. This Guidance is primarily focused on studies designed to test prespecified hypotheses, as opposed to hypothesis-generating studies, and emphasizes that investigators should submit protocols to FDA before study initiation and final reports upon completion.¹¹ FDA anticipates applying many of

¹⁰ See FDA guidance [E 10 Choice of Control Group and Related Issues in Clinical Trials](#).

¹¹ Recent recommendations on good study practices from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) characterize hypothesis-generating studies as exploratory studies. These are studies that do not hypothesize the presence of a specific treatment effect or its magnitude, but primarily serve as a first step to learn about possible treatment effects. In contrast, Hypothesis Evaluating Treatment Effectiveness (HETE) studies are defined as studies that evaluate the presence or absence of a prespecified effect or its magnitude and are designed to test a specific hypothesis in a specific population (Berget et al. 2017). HETE studies, as defined by ISPOR/ISPE, are the primary focus of the Pharmacoepidemiologic Guidance.

the principles outlined in that guidance when evaluating observational studies to support changes in labeling that are within the scope of this framework (i.e., those that require evidence of effectiveness).

In considering whether data gathered through observational study designs are appropriate to generate RWE for the purpose of supporting effectiveness determinations, FDA intends to evaluate multiple questions of interest that could affect the ability to draw a reliable causal inference, including, for example, the role of existing evidence (e.g., the natural history of the disease) and how the inclusion of a more diverse population can result in a heterogeneity of treatment effects making it difficult to detect smaller effect sizes.

In the context of retrospective observational studies using RWD, FDA will focus on critical questions such as the following:

1. What are the characteristics of the data (e.g., contain data on a relevant endpoint, consistency in documentation, lack of missing data) that improve the chance of a valid result?
2. What are the characteristics of the study design and analysis that improve the chance of a valid result?
 - a. Can an active comparator improve the chance of a valid result?
 - b. Given potential unmeasured confounders in non-randomized RWD studies, as well as potential measurement variability in RWD, is there a role for non-inferiority designs?
3. What sensitivity analyses and statistical diagnostics should be pre-specified for observational studies using RWD to generate RWE for effectiveness?

In addition to study design and data considerations, transparency about study design and analysis before execution is critical for ensuring confidence in the results. *ClinicalTrials.gov* was established to promote transparency by requiring many clinical trials to be registered publicly on this website and to post certain summary trial results after the trial is complete.¹² Currently, there is no similar reporting requirement for observational studies, although parties can voluntarily register observational studies on ClinicalTrials.gov.

¹² For more information about registration and display, see <https://clinicaltrials.gov/>.

The potential lack of up-front transparency, especially in retrospective observational study design and conduct, coupled with the fact that retrospective analyses in electronic datasets can be conducted multiple times relatively inexpensively with varying study design elements, makes it possible to conduct numerous retrospective studies until the desired result is obtained and then submit only favorable results as if they were the result of a single study with a prespecified protocol. FDA will consider policies to prevent such practices, including recommendations from experts and other stakeholders. For example, FDA will consider the recently published task force recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) on good procedural practices for treatment effectiveness studies, including transparency and reproducibility (Berger et al. 2017; Wang et al. 2017). FDA will also explore whether differences in retrospective and prospective observational designs require different approaches.

Program Item. Adapting and building on the Pharmacoepidemiologic Guidance, FDA plans to issue guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision-making. FDA will also consider reporting requirements for such studies used to support effectiveness determinations.

Regulatory Considerations for Study Designs Using RWD

The use of EHRs, mobile health technology, and other electronic data-capture technology, together with new trial and study designs using RWD, has the potential to streamline and improve the efficiency of clinical studies. Nevertheless, these advances may also raise new questions about the applicability of certain regulatory requirements, including requirements for informed consent and appropriate oversight and monitoring. To facilitate the electronic capture of data from health care systems for research purposes while maintaining adequate documentation for FDA to validate the source and reliability of the data, FDA has already provided guidance on the use of electronic source data, electronic signatures, and EHRs. FDA has also issued the guidance [*Use of Electronic Informed Consent Questions and Answers*](#) in December 2016 on using electronic informed consent. Additional guidance may be needed to address different study designs using RWD to generate RWE for effectiveness determinations.



Use of Electronic Source Data

There are several FDA guidance documents that address the use of electronic data in clinical investigations. In September 2013, FDA published the guidance [*Electronic Source Data in Clinical Investigations*](#), which promotes capturing source data in electronic format and provides recommendations on the capture, review, and retention of electronic source data in FDA-regulated clinical investigations. In July 2018, FDA published the final guidance [*Use of Electronic Health Records in Clinical Investigations*](#). This guidance provides recommendations on ensuring the integrity of EHR data that are collected and used as electronic source data in clinical investigations of medical products.

FDA's Part 11 regulations (21 CFR part 11) focus on the quality, authenticity, and reliability of electronic records from their point of creation to their modification, maintenance, archiving, retrieval, or transmission. In June 2017, FDA published a draft guidance [*Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 - Questions and Answers*](#). This guidance discusses procedures to help ensure that electronic records and electronic signatures are trustworthy and reliable and proposes a risk-based approach when deciding to validate electronic systems, implement audit trails for electronic records, and archive records that are pertinent to clinical investigations.

Program Item. FDA will consider whether these guidance documents adequately address concerns relevant to different study designs using RWD to generate RWE for drug product effectiveness determinations or whether additional guidance on use of electronic source data is needed.

Regulatory Considerations for Clinical Studies Generating RWE

FDA will also examine how **FDA's regulatory requirements are applied to data from randomized clinical trials that are integrated into the health care system and observational studies when they are intended to generate RWE for regulatory decision-making.** For example, we will examine the use of risk-based¹³ and central monitoring for clinical trials that are integrated into the health care system.

In addition, there are multiple guidance documents that address FDA inspections, recordkeeping, and record retention requirements for regulated entities within the clinical trial enterprise. FDA will consider whether currently available guidance adequately addresses inspection-related concerns relevant to different sources of RWD used to generate RWE regarding the safety and effectiveness of drug products (e.g., informed consent, system access, records that must be available and viewable for review upon request at an FDA inspection).

Other regulatory considerations outside of FDA's authority may affect the acquisition and use of RWD, including the [Health Insurance Portability and Accountability Act](#) (HIPAA), but these will not be addressed within the FDA framework.

Program Item. FDA plans to finalize the guidance *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR part 11 - Questions and Answers* and consider its applicability to different study designs. FDA will also issue additional guidance as needed on regulatory considerations raised by different study designs using RWD to generate RWE that is submitted to support drug product effectiveness.

¹³ FDA issued the guidance [Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring](#) in August 2013.

Data Standards — Appropriate Data Standards for Integration and Submission to FDA

Along with other activities under FDA's RWE Program, FDA will assess the data standards and implementation strategies required to use RWD/RWE at FDA, identify any gaps between those requirements and existing FDA systems, and recommend a path forward to ensure that RWD/RWE solutions are an integral part of the full drug development and regulatory life cycle at FDA. Activities for this work include:

- Identify data standards and implementation considerations that apply to proposed uses of RWD/RWE at FDA
- Review existing RWD/RWE-driven work, both internally and with external stakeholders, to identify gaps that need to be addressed
 - This evaluation could include projects such as development and use of relevant data standards, implementation strategies for applications and databases to connect with RWD sources, and strategies for coping with variations in data quality.
- Collaborate with internal and external stakeholders to adapt or develop standards and implementation strategies for RWD/RWE-driven solutions at FDA
- Integrate RWD/RWE-driven solutions with existing FDA systems
 - This activity could include assessment of topics such as Health IT strategies for RWD receipt and processing for potential use at FDA, impact on reviewer workload, and tools and training needed for FDA reviewers.

Stakeholder Engagement

Stakeholder engagement has been, and will continue to be, an important part of FDA's RWE Program. In addition to FDA's stakeholder engagement initiatives outlined in this section, the Appendix details research demonstration projects with stakeholders to facilitate the use of RWE in regulatory decision-making.

“The efforts of the FDA should provide insights regarding potential uses of RWE for regulatory decisions, but are just one aspect of a larger challenge. If RWD and RWE are to be effectively leveraged for public health purposes, there will need to be shared learning and collaboration across clinicians, patients, health care systems, pharmaceutical companies, and regulators.”

Corrigan-Curay, J., Sacks, L., and Woodcock, J.
JAMA Viewpoint, September 4, 2018

Internal Engagement. In December 2017, FDA launched an internal website and outreach effort to engage FDA staff in activities supporting FDA's program to evaluate the use of RWE for regulatory decisions. At the center of this effort was the launch of the RWE Subcommittee of CDER's Medical Policy and Program Review Council, which includes leadership across CDER and CBER. The RWE Subcommittee will serve as a cross-cutting forum for RWE issues and will focus on CDER's evaluation of RWE and guide policy development. Staff from the Office of New Drugs may consult with the RWE Subcommittee when evaluating the use of RWD and RWE to inform regulatory decisions about product effectiveness. The RWE Subcommittee will provide advisory recommendations as needed on whether underlying data, methods, and other study design elements are appropriate to provide support for a regulatory decision. The Subcommittee will also provide review divisions with additional resources to evaluate the use of RWE, consider how stakeholders propose to use RWE, and identify areas in which policy development will facilitate consistent practices.

External Engagement. In September 2017, through its cooperative agreement with the Duke Margolis Center for Health Policy, FDA convened a public meeting that explored the use of RWE for regulatory decisions.¹⁴ Representatives from industry, academia, patient advocacy groups, and other stakeholders discussed, among other things, opportunities and challenges associated with applying RWD and RWE

¹⁴ This meeting satisfies a PDUFA VI commitment to gather input on topics related to the use of RWE for regulatory decision-making.

to demonstrate product effectiveness, including the data acquisition, study design, and analytic methods necessary to establish causal inference. The workshop informed development of FDA's RWE framework.

FDA is also engaged in a [project](#) by the Clinical Trial Transformation Initiative (CTTI)¹⁵ to evaluate the use of RWD in randomized trials to generate RWE about medical products.

In addition, through the National Academy of Sciences, Engineering, and Medicine, FDA supported a three-series workshop titled "Examining the Impact of Real World Evidence on Medical Product Development." FDA staff engaged in the planning of each workshop, and FDA leadership participated in these workshops.

- September 2017 — [Workshop 1: Incentives](#)
- March 2018 — [Workshop 2: Practical Approaches](#)
- July 2018 — [Workshop 3: Application](#)

FDA will continue to engage stakeholders through public meetings and other forums as part of its RWE Program.



Conclusion

FDA will continue its efforts to evaluate and explore ways and methods to optimize the utility of RWE. FDA has developed this Framework to guide its RWE Program. FDA already has taken the initiative to pilot projects that further the understanding of potential uses of RWD and RWE and will continue these efforts. Throughout this process, FDA is making stakeholder engagement a key aspect of its RWE Program.

¹⁵ CTTI was established by FDA and Duke University as a public-private partnership in 2007. It comprises more than 80-member organizations and several individual patient/caregiver representatives working to identify and promote practices that will increase the quality and efficiency of clinical trials.

Glossary

Case Report Form (CRF): a specialized document in clinical research that is protocol driven and is used to collect the essential information for a clinical trial on each participant. All data on each patient participating in a clinical trial are documented in the CRF. CRFs can be in paper or electronic form.

Clinical Trial: a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Clinical trials are interventional clinical studies.

ClinicalTrials.gov: a data bank established to promote transparency by requiring many clinical trials to be registered publicly on the ClinicalTrials.gov website and to post certain summary trial results after the trial is complete.

Data Standard: a set of rules about how a particular type of data should be structured, defined, formatted, or exchanged between computer systems. Data standards make submissions predictable, consistent, and have a form that an information technology system or a scientific tool can use.

Medical Claims Data: the compilation of information from medical claims that health care providers submit to insurers to receive payment for treatments and other interventions. Medical claims data use standardized medical codes, such as the World Health Organization's International Classification of Diseases Coding (ICD-CM), to identify diagnoses and treatments.

Observational Study: a non-interventional clinical study design that is not considered a clinical trial.

Observational Study, Prospective: a study in which the population of interest is identified at the start of the study, and exposure/treatment and outcome data are collected from that point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated.

Observational Study, Retrospective: a study that identifies the population and determines the exposure/treatment from historical data (i.e., data generated before the initiation of the study). The variables and outcomes of interest are determined at the time the study is designed.

Patient 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 purpose. Registries are generally defined either by diagnosis of a disease (disease registry) or usage of a drug, device, or other treatment (exposure registry).

Patient Reported Outcome (PRO): a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response.

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

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

Sentinel Initiative: a long-term effort to create a national electronic system for monitoring FDA-regulated medical products.

Sentinel System: a system being developed and implemented in stages, to expand FDA's existing postmarket safety surveillance capabilities by enabling FDA to actively gather information about the safety of regulated medical products once they reach the market.

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FDA Guidances Noted in this Document

- In August 2017, FDA issued the guidance [*Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*](#). This guidance clarifies how the FDA evaluates real-world data to determine whether they are sufficient for generating the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices.
- In May 2013, FDA issued the guidance [*Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*](#) (Pharmacoepidemiologic Guidance). This guidance includes recommendations for evaluating the data sources used in pharmacoepidemiologic safety studies.
- In December 2009, FDA issued the guidance [*Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*](#). This guidance describes how the FDA reviews and evaluates existing, modified, or newly created PRO instruments used to support claims in approved medical product labeling.
- In May 2001, FDA issued the guidance [*E 10 Choice of Control Group and Related Issues in Clinical Trials*](#). This guidance is intended to assist applicants in choosing a control group for clinical trials intended to demonstrate the efficacy of a treatment.
- In December 2016, FDA issued the guidance [*Use of Electronic Informed Consent Questions and Answers*](#). This guidance provides recommendations on the use of electronic systems and processes that employ multiple electronic media to obtain informed consent for both HHS-regulated human subject research and FDA-regulated clinical investigations of medical products.
- In September 2013, FDA issued the guidance [*Electronic Source Data in Clinical Investigations*](#). This guidance promotes capturing source data in electronic format and provides recommendations on the capture, review, and retention of electronic source data in FDA-regulated clinical investigations.
- In July 2018, FDA issued the guidance [*Use of Electronic Health Records in Clinical Investigations*](#). This guidance provides recommendations on ensuring the integrity of EHR data that are collected and used as electronic source data in clinical investigations of medical products.
- In June 2017, FDA issued the draft guidance [*Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 - Questions and Answers*](#). This guidance discusses procedures to help ensure that electronic records and electronic signatures are trustworthy and reliable and proposes a risk-based approach when deciding to validate electronic systems, implement audit trails for electronic records, and archive records that are pertinent to clinical investigations.
- In August 2013, FDA issued the guidance [*Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring*](#). This guidance assists sponsors of clinical investigations in developing risk-based monitoring strategies and plans for investigational studies of medical products.

Appendix

DEMONSTRATION PROJECTS

The following are demonstration projects that FDA is funding to inform the Agency about the use of RWD and RWE.

Current Demonstration Projects to Inform Assessment of Fitness for Use in Regulatory Decisions

[Standardization and Querying of Data Quality Metrics and Characteristics for Electronic Health Data](#): One of the challenges in using data from EHRs is that no standards exist for describing the quality and completeness of electronic health data. Understanding the characteristics of a data source is critical for investigators in their determination about whether the data are fit for a specific use. Effective use of the growing number of data sources and distributed networks will require adoption of a uniform approach to describing the quality characteristics of electronic health data, as well as the data capture characteristics at the institutional, provider, and health plan levels and data domain level. FDA is supporting a project to develop, test, and implement a standards-based approach to describing data characteristics and quality and presenting relevant metrics.

[Source Data Capture from EHRs: Using Standardized Clinical Research Data](#): Another challenge with using EHRs is that they were developed for clinical care, not clinical research. Despite overlap in the information needed for both, the way information is captured may not always be optimized for research use. FDA is collaborating with the University of California in San Francisco's (UCSF) Carol Franc Buck Breast Care Center on developing the source data capture from EHRs (One Source) program.

This project will demonstrate a single-point, data capture approach from the EHR to an electronic data capture system (EDC) using open, consensus-based standards. This could allow data collected in the EHR to be used as part of an FDA-regulated clinical trial, eliminating the need for duplicate entry, and potentially saving time, money, and eliminating an opportunity for errors. This project will provide a cloud-based HIPAA and 21 CFR Part 11-compliant tool for researchers of patient-centered outcomes to seamlessly integrate EHR and EDC systems.

[HARMONY-OUTCOMES Ancillary Study \(NCT02465515\)](#): FDA is supporting research to examine the feasibility of using EHRs in clinical research. Through a collaboration between the Duke Clinical Research Institute and GlaxoSmithKline (GSK), the HARMONY-OUTCOMES Ancillary Study will examine how EHRs at selected trial sites in GSK's cardiovascular outcome trial for albiglutide could have been used to identify eligible participants, populate baseline characteristics of participants into an electronic CRF, and identify clinical endpoints (O'Brien and Curtis 2017).

[INFORMED Collaborations in Oncology](#): FDA is collaborating on the use of RWD to generate RWE. For example, as part of the Information Exchange and Data Transformation ([INFORMED](#)), the [Oncology Center for Excellence](#) is collaborating with [Flatiron Health](#) to examine how RWD can be used to gain insights regarding the safety and effectiveness of new cancer therapies (Khozin et al. 2018). In addition, in June 2017, FDA's partnership with [CancerLinQ](#), the American Society of Clinical Oncology's big data initiative, was [announced](#). FDA and CancerLinQ will be using real-world, aggregate, de-identified patient care data from oncology practices to look at a variety of issues related to the appropriate use of newly approved therapies. The initial focus will be on immunotherapy agents approved for melanoma. By working with these data to explore questions around the use of new oncologic agents, FDA will better understand how to evaluate the relevance and quality of these data.

[FDA-Catalyst Program](#): The FDA-Catalyst is an initiative that leverages the Sentinel infrastructure and other capabilities of the Sentinel System while supplementing it with data from interventions or interactions with health plan members, providers, or both. FDA-Catalyst provides a platform to answer a wider range of questions than can be addressed by the Sentinel System data alone.

[FDA MyStudies — Mobile Application](#): As part of the FDA-Catalyst program, the *FDA MyStudies* mobile device application was developed to support informed consent as well as secure data collection from patients at multiple study sites or data partners in real time. Specified administrators can download patient responses from a patient data storage environment that is compliant with the HIPAA and Federal Information Security Management Act and can be linked to existing electronic health data. The code for *MyStudies* is open source so software developers can improve upon its capabilities. *MyStudies* has an associated web-based study design portal that allows for the creation, distribution, and modification of questionnaires so it can be configured for different therapeutic areas and health outcomes, which reduces software development hurdles for non-FDA users. As an initial proof of

concept for drug safety and effectiveness research, pregnant women used the app to provide information on exposures such as prescription and OTC drug use and health care outcomes during the last quarter of 2017.

Current Demonstration Projects to Inform Assessment of Study Designs Using RWD to Support Effectiveness

[Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation \(IMPACT-AFib\) \(NCT02082548\)](#): Through FDA-Catalyst, FDA is currently supporting a randomized trial using data from the Sentinel System to test whether a patient and provider educational intervention can increase anticoagulant use for individuals who, per the data within the Sentinel System, have atrial fibrillation and are at increased risk of stroke. Not only is this a critical public health question, it is also a proof of concept trial for conducting interventional effectiveness trials using the Sentinel infrastructure.

[Hepatitis C Therapeutic Registry and Research Network \(HCV-TARGET\)](#): HCV-TARGET is an international research consortium created to inform the ongoing transformation of hepatitis C treatment and research. HCV-TARGET includes 112 academic and community sites in 31 states, Puerto Rico, Canada, and Europe as well as partnerships with multiple industry sponsors, FDA, and the patient advocacy community. In 2011, HCV-TARGET established a national registry to observe patients undergoing hepatitis C treatment and coordinate real-world monitoring on a national scale for new therapies as they enter the market. Since inception in 2011, HCV-TARGET has enrolled more than 10,000 patients treated with HCV direct-acting antiviral-based regimens approved by FDA (Mishra et al. 2017).

Effectiveness Research with Real World Data to Support FDA's Regulatory Decision-Making: In May 2018 FDA launched a partnership the Brigham and Women's Hospital/Harvard Medical School that aims to identify and reproduce a representative set of approximately 30 phase 3/4 randomized control trials with observational RWD analyses to delineate the circumstances under which observational studies using existing electronic administrative health care data can replicate the results of clinical trials. The investigators will develop and make a scalable analytics platform available to FDA staff for evaluation of RWD utility.

Current Demonstration Projects on Data Standards and Use of RWD

Common Data Model (CDM) Harmonization Project: Various initiatives have created networks of RWD to capture data across health care delivery systems. Participating organizations within these networks map their databases to a CDM that provides consistent format and content. This project seeks to develop a meta-CDM that enables a researcher to make a single query that is usable across four large RWD networks: FDA's Sentinel System, the Observational Health Data Sciences and Informatics (OHDSI), PCORnet, and the Accrual of Patients to Clinical Trials Network (ACT)/ Informatics for Integrating Biology & the Bedside (i2b2). This project is aimed to achieve a sustainable data network infrastructure, promote interoperability and foster the creation of a Learning Health System. An [overview of the project](#) is accessible on the OHDSI website.



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