



Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry

Real-World Data Guidance Webinar Series

February 11, 2022

11 am – 12 pm Eastern Time

This webinar is part of a series hosted by the Reagan-Udall Foundation for the FDA, in collaboration with the U.S. Food and Drug Administration (FDA). This series is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of \$56,097 in federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit [FDA.gov](https://www.fda.gov).



Welcome

Susan C. Winckler, RPh, Esq.
Reagan-Udall Foundation for the FDA

Thank you for joining

This webinar is being recorded. The slides and video recording will be available after the meeting.

If you'd like to ask a question, you may enter it in the Zoom Q&A. We will get to as many questions as time allows.

Speakers and presenters will not address questions regarding any pending regulatory action.

Submit either electronic or written comments on the draft guidance March 9, 2022 to [Docket Number FDA-2021-D-1214](#) to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.



Agenda

11 am

Welcome

11:05 am

Opening Remarks

11:10 pm

Overview of Draft Guidance

11:40 am

Question and Answer Panel

11:55 am

Closing Remarks

12 pm

Adjourn

All times listed in Eastern Time

RWD/RWE Guidance Webinar Series



Webinar 1 (November 4, 2021): Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

Webinar 2 (December 3, 2021): Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Webinar 3 (January 28, 2022): Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Webinar 4 (February 11, 2022): Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

If you are interested in viewing the recording of the webinars about the guidances listed on the screen, please visit the FDA Foundation website at reaganudall.org

Why Are We Here Today?

Provide an overview and address questions from the public about the draft guidance titled [*Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products.*](#)

Submit comments on the draft guidance by March 9, 2022, to [Docket Number FDA-2021-D-1214](#) to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance



Opening Remarks

John Concato, MD, MS, MPH

Associate Director for Real-World Evidence
Analytics, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Public Webinar

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

11 February 2022

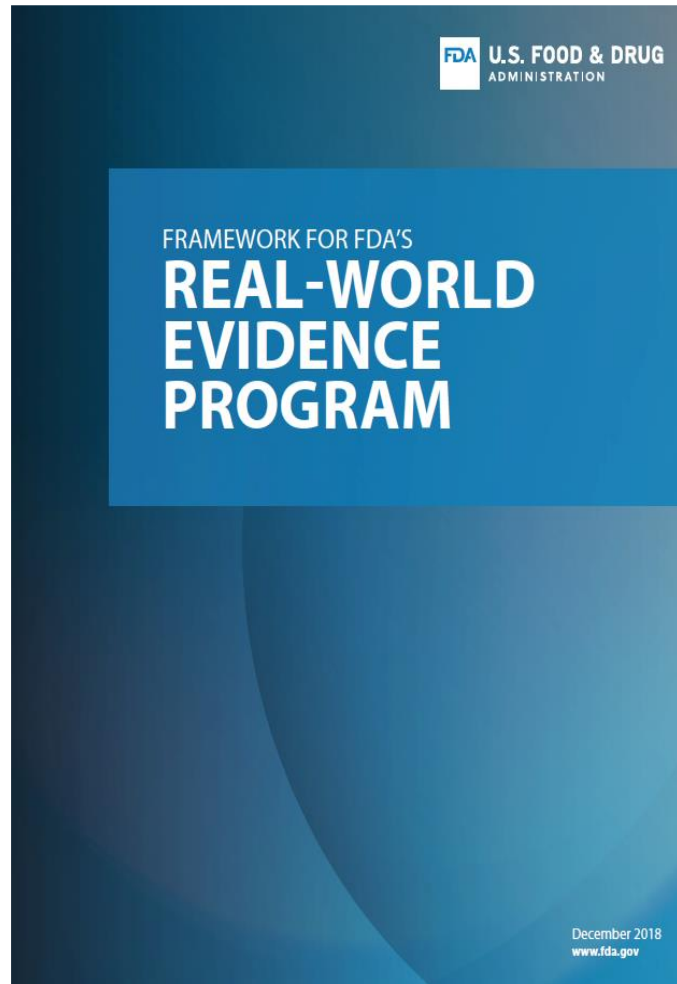
John Concato, MD, MS, MPH

Associate Director for Real-World Evidence Analytics
Office of Medical Policy, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

21st Century Cures Act of 2016 – *status as of Feb 2022*







- **FDA *has established* a program to evaluate the potential use of real-world evidence (RWE) to:**
 - **Support new indication for a drug approved under section 505(c)**
 - **Satisfy post-approval study requirements**
- **Standard for substantial evidence *remains unchanged*; commitments under Prescription Drug User Fee Act (PDUFA) VI**
- **Draft framework *issued December 2018***
 - **Describes sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry *issued Sep, Oct, Nov, & Dec 2021***
 - **Others in development**



- **Applies to Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)**
- **Multifaceted program to implement RWE:**
 - internal processes
 - external stakeholder engagement
 - demonstration projects
 - guidance development ←

CDER Guidance Agenda New & Revised Draft Guidance Documents Planned for Publication in Calendar Year 2021¹

CATEGORY – Real World Data/Real World Evidence (RWD/RWE)²

-  • Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
-  • Data Standards for Drug and Biological Product Submissions Containing Real-World Data
-  • Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
-  • Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

¹ Final guidance documents planned for publication in calendar year 2021 are not included on this list. CDER is not bound by this list of topics, nor required to issue every guidance document on this list. We are not precluded from developing guidance documents on topics not on this list.

² New category added since the January 2021 posting

Considerations for the Use of Real-World Data and Real- World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

December 2021
Real World Data/Real World Evidence (RWD/RWE)



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Associate Director for Policy Analysis,
Office of Medical Policy Initiatives, Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Overview of Draft Guidance

Stefanie Kraus, JD

Senior Regulatory Counsel, Office of Regulatory Policy
Center for Drug Evaluation and Research
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Public Webinar

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

11 February 2022

Tala Fakhouri, PhD, MPH

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Considerations for the Use of Real-World Data and Real- World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2021
Real World Data/Real World Evidence (RWD/RWE)

This Guidance:

- **Focuses primarily on clinical study designs that are non-interventional (observational) studies**
- **Discusses applicability of 21 CFR Part 312 (Investigational New Drug Application) to studies involving the use of real-world data (RWD)**
- **Provides regulatory considerations for non-interventional (observational) studies involving the use of RWD**

- **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 about the usage and potential benefits or risks of a medical product derived from analysis of RWD
- **Interventional study (clinical trial)**: a study in which participants are assigned to one or more interventions according to a study protocol, to evaluate the effects of those interventions on subsequent health-related biomedical or behavioral outcomes
- **Non-interventional study (observational study)**: a study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol

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 - B. Regulatory Considerations for Non-Interventional (Observational) Studies**
 - 1. Overview**
 - 2. Transparency Regarding Data Collection and Analysis**
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**Definitions of RWD
and RWE**

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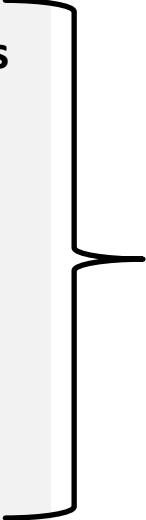
→ **Definitions of
interventional and
non-interventional
study designs**

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- **RWD utilized in both interventional and non-interventional study designs**
- **If an interventional study meets the definition of a clinical investigation under §312.3, then it is subject to FDA regulations under part 312**

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Regulatory considerations for the use of RWD in non-interventional study designs

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Overview Section

- **A marketing application to support safety/effectiveness of a drug must satisfy applicable legal standards for the application to be approved or licensed**
- **Two general types of non-interventional studies, those that:**
 - 1. involve *only* the analysis of data reflecting the use of a marketed drug in routine practice**
 - 2. include ancillary protocol-specified activities or procedures (e.g., questionnaires, lab tests, imaging studies)**
 - **FDA does not consider these types of studies to be clinical investigations under 21 CFR part 312**
 - **Nonetheless, protection of human subjects under these circumstances is critical, and sponsors must ensure that applicable requirements per FDA regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards) are met**

Overview Section (cont'd)

- **Sponsors should consult with data privacy experts on non-interventional study protocols, as such experts may help identify and address data privacy and security concerns raised when accessing health care data**

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Transparency Regarding Data Collection and Analysis

- **Early engagement**: Sponsors should engage with FDA in the early stages of designing a non-interventional study:
 - Request a Type C meeting
 - Provide draft versions of the protocol and statistical analysis plan (SAP) prior to finalizing the documents and before conducting study analyses
- **Study protocol and SAP**: FDA must be confident that data sources/databases are not selected, and specific analyses conducted, to favor a certain conclusion:
 - Sponsor should provide evidence that the protocol and SAP were finalized prior to reviewing outcome data and before performing the prespecified analyses
 - Any revisions to the protocol should be date-stamped, and the rationale for each change should be provided

- **Data source selection**: Access to and evaluation of relevant data sources or databases are important steps in evaluating a study's feasibility
 - Evaluations of data sources or databases for study design or feasibility purposes serve to (1) learn about the suitability of the data to address the research question being posed, and (2) estimate the statistical precision of a potential study without evaluating outcomes
 - Sponsors should:
 - describe in the study protocol all data sources accessed when designing the study-and results of feasibility evaluations or exploratory analyses
 - Provide justification for selecting or excluding relevant data sources
 - generate audit trails in their datasets that can track access to, and analyses performed on, relevant data sources

Transparency Regarding Data Collection and Analysis

- **Documentation:**
 - Sponsors should document all analyses performed on the data during the study design phase, including feasibility evaluations and exploratory analyses
 - Sponsors should also demonstrate that the choice of the final analytic dataset and the conduct of final analyses align with the research question of interest and do not favor particular study findings
- **Inclusion and exclusion:**
 - Sponsors should describe patient characteristics of the source population (i.e., the population from which the study population is drawn) and the study population (i.e., the population for which analyses are conducted), and note any differences that may impact the final study findings

Transparency Regarding Data Collection and Analysis

- **Study registration**: To ensure transparency regarding their study design, sponsors should post their study protocols on a publicly available website, such as:
 - **ClinicalTrials.gov**
 - **European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for post-authorization studies**

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Data Access

- **Submission of patient level data:**
 - In the early stages of study design, sponsors should discuss with the relevant review division the expectations regarding access to RWD
 - Sponsors must ensure that they are able to submit patient-level data for any RWD that have been analyzed as part of the clinical study included in a marketing application when required under 21 CFR 314.50 and 601.2
- **Third party vendors:**
 - If certain RWD are owned and controlled by third parties, sponsors should have agreements in place to ensure that relevant patient-level data can be provided to FDA and source data necessary to verify the RWD are available for inspection

- **Programming codes and algorithms**: Sponsors should ensure that RWD and associated programming codes/algorithms submitted to FDA are documented, well-annotated, and complete, allowing FDA to replicate the study analysis

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- **Study monitoring by type of non-interventional study:**
 - If no additional ancillary activities, study monitoring may be focused on maintaining the reliability of the RWD and data integrity, beginning with extraction of the data from its origin (i.e., data accrual) through data curation and transformation and reporting of results
 - If additional protocol-specified activities and procedures, study monitoring should also ensure that applicable human subject protections are met and data integrity is maintained
- **Risk-based quality management approach:**
 - FDA encourages a risk-based quality management approach to study oversight, focused on preventing or mitigating important and likely risks to study quality and on processes critical to human subject protection

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- **Postmarketing safety reporting:**
 - **Given that non-interventional studies examine the use of a drug in routine medical practice, relevant adverse events should be submitted to FDA in accordance with postmarketing safety reporting regulations**
 - **Sponsors will often use only a subset of a larger real-world dataset to conduct analyses to support labeling changes:**
 - **FDA does not expect the sponsor to search the entire database regarding all uses of the product for adverse events that would meet the reporting requirements under FDA's regulations**
 - **Nonetheless, if a sponsor identifies adverse events that are subject to postmarketing reporting requirements during the course of conducting a non-interventional study, such events must be reported**

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Other Sponsor Responsibilities

- **21 CFR part 11**: Electronic systems used by the sponsor to manage data and to produce required records must comply with 21 CFR part 11
- **Other sponsor responsibilities**: Sponsors should take responsibility for all activities related to the design, conduct, and oversight of the studies, including:
 - Select researchers qualified by training and experience, and confirm that researchers have the appropriate skills and information
 - Ensure that the study is conducted in accordance with the final protocol and SAP and documenting any deviations
 - Maintain and retain adequate study records
 - Ensure that FDA can access and verify relevant records (e.g., source records)
 - Ensure appropriate monitoring of the study, including selecting a monitor qualified by training and experience for studies requiring additional data collection

Other Sponsor Responsibilities

- **Information on Researchers:** Sponsors should retain and make available upon request a log of any researcher(s) who have significant involvement in the design or conduct of the study. The log should contain:
 - Researcher's name and affiliations
 - Description of roles or activities performed
 - Qualifications regarding education, training, and experience
- **Third parties:** If sponsors engage third parties to perform study-related tasks:
 - Sponsors should document the roles/responsibilities of the organization(s) performing the tasks
 - Sponsors should remain responsible for all study-related activities unless a sponsor has transferred its responsibility to a contract research organization

Submitting Comments

- **Submit either electronic or written comments on the draft guidance to **Docket No. FDA-2021-D-1214** by March 9th, 2022**
- **Electronic submissions**
 - **Federal eRulemaking Portal (<https://www.regulations.gov>)**
- **Written submissions**
 - **Mail/Hand Delivery/Courier to Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852**

Acknowledgments

- **FDA Center for Drug Evaluation and Research**
 - **Office of Medical Policy**
 - **Office of New Drugs**
 - **Office of Regulatory Policy**
 - **Office of Strategic Programs**
 - **Office of Surveillance and Epidemiology**
 - **Office of Translational Science**
- **FDA Center for Biologics Evaluation and Research**
- **FDA Oncology Center of Excellence**
- **Center for Devices and Radiological Health**

THANK YOU



U.S. FOOD & DRUG
ADMINISTRATION

Question and Answer

Moderated by

Susan C. Winckler, RPh, Esq.

Panelists

John Concato, MD, MS, MPH

Tala Fakhouri, PhD, MPH

Stefanie Kraus, JD, MPH

Next Steps

Submit either electronic or written comments on the draft guidance by March 9, 2022, to [Docket Number FDA-2021-D-1214](#) to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

Thank you!