Considerations Regarding Non-Interventional Studies for Drug and Biological Products

The public meeting will begin shortly

Real-World Evidence Guidance Webinar Series

May 30, 2024, from 2-2:45 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

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 $75,417 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.

Housekeeping

REAGAN-UDALL FOUNDATION FOR THE FDA

Due to the meeting size, your microphone and video will remain off during the meeting.

This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website after the meeting.

Please share your questions and comments for the speakers using the Zoom Q&A function.

Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

2 pm	Welcome
2:05 pm	Opening Remarks
2:10 pm	Overview of Draft Guidance
2:25 pm	Questions and Answer
2:40 pm	Closing Remarks
2:45 pm	Adjourn

RWD/RWE Guidance Webinar Series

REAGAN-UDALL FOUNDATION FOR THE FDA

1. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (November 4, 2021)
2. Data Standards for Drug and Biological Product Submissions Containing Real-World Data (December 3, 2021)
3. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (January 28, 2022)
4. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (February 11, 2022)
5. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (April 13, 2023)
6. **Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products (May 30, 2024)**

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?

REAGAN-UDALL FOUNDATION FOR THE FDA

Provide an overview and address questions from the public about the draft guidance titled *Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products.*

Submit comments on the draft guidance by June 18, 2024, to https://www.regulations.gov/docket/FDA-2023-D-5470 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

REAGAN-UDALL FOUNDATION FOR THE FDA

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

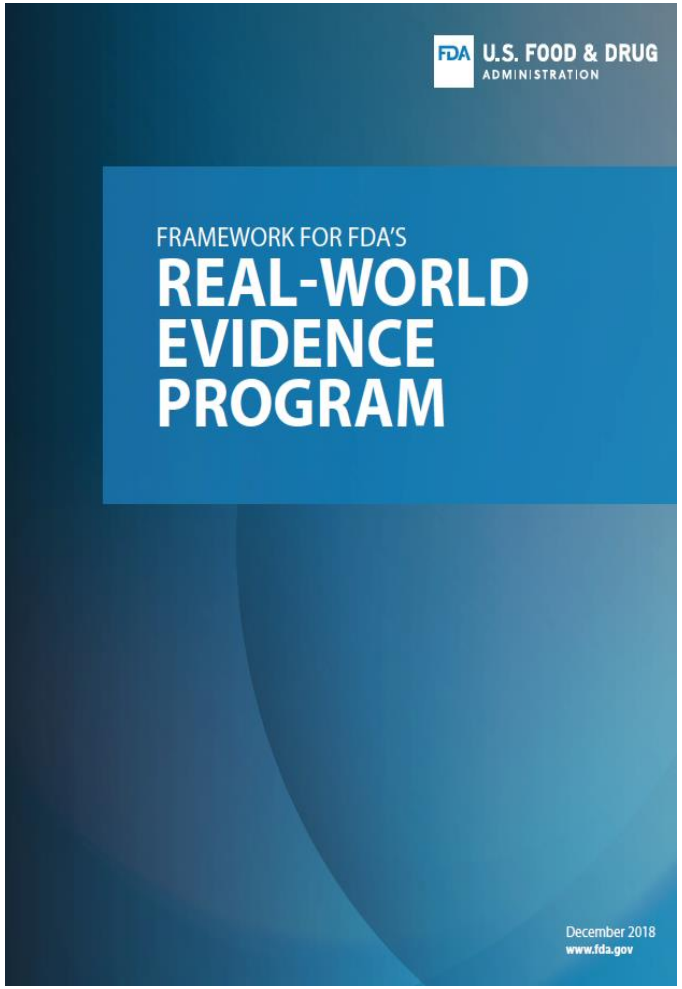
Public Webinar

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

30 May 2024

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

FDA's RWE Framework For Drugs & Biologics (2018)



- **Center for Drug Evaluation & Research (CDER); Center for Biologics Evaluation & Research (CBER); & Oncology Center of Excellence (OCE)**
- ***Center for Devices & Radiological Health (CDRH) has separate regulations and RWE program***
- **Multifaceted program to implement RWE:**
  - **internal agency processes (e.g., consults)**
  - **external engagements (e.g., "listening sessions")**
  - **demonstration projects (e.g., U01 awards)**
  - **guidance development (also address mandates)**

https://www.fda.gov/media/120060/download

Terms for Study Design

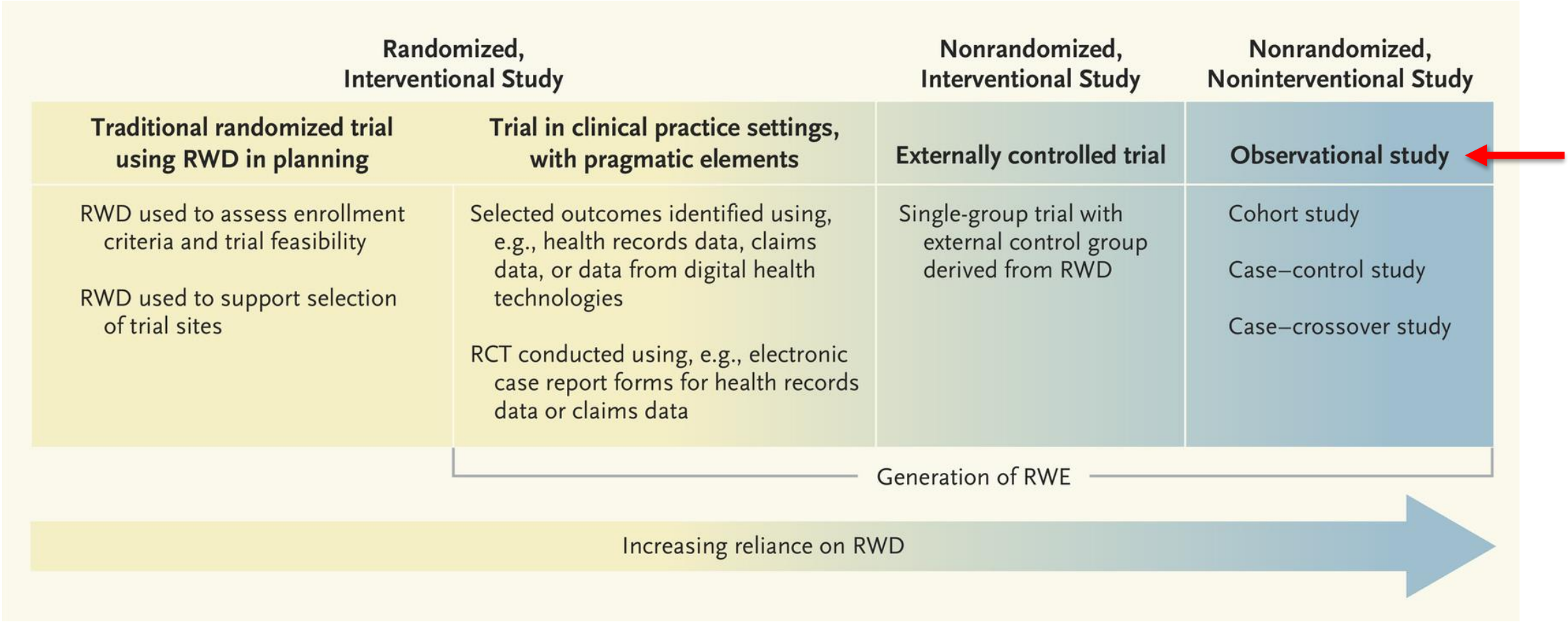
Interventional study (clinical trial): participants assigned to treatment by study protocol

Non-interventional (observational) study: patients receive treatment during routine medical care, even if laboratory or imaging procedures are done per research protocol

‘Landscape’ of RWD & RWE

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.



Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

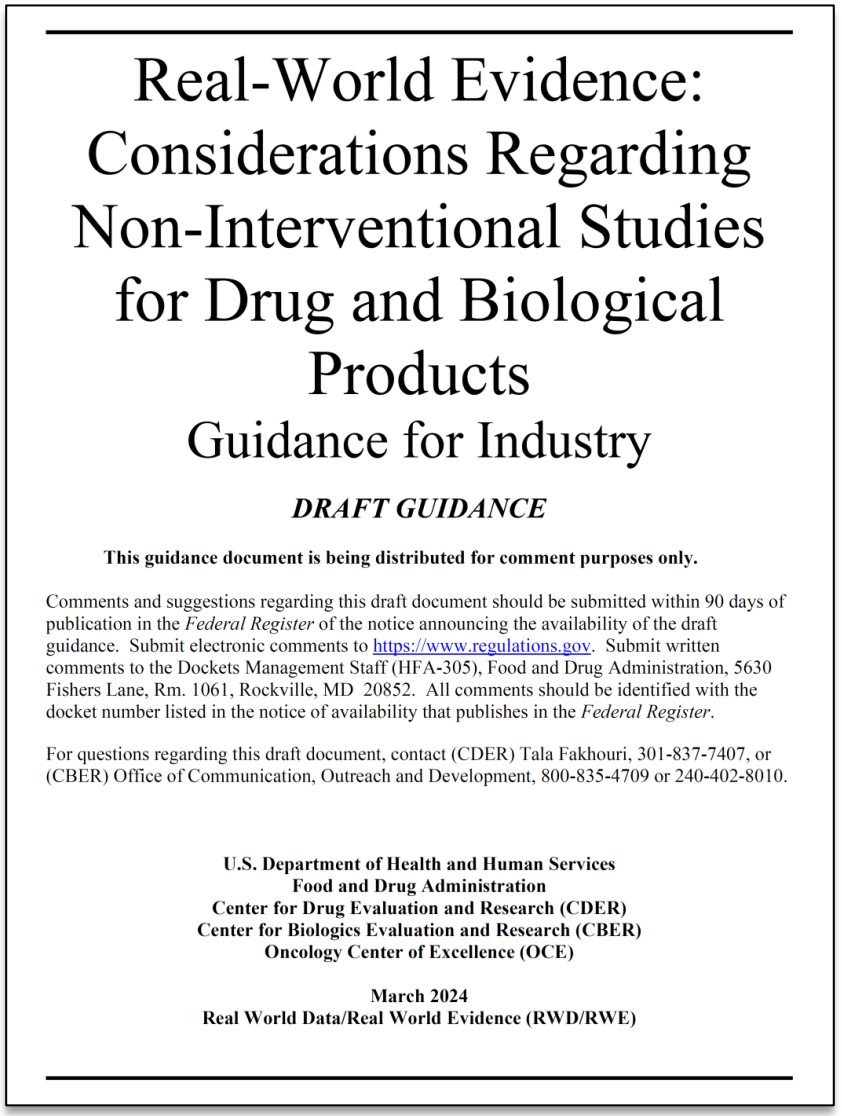
N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

FDA RWE Guidance (2021-2024)

Topic	Category	Status
Submitting RWE	Procedural	final issued
EHRs and claims data	Data considerations	draft issued
Registry data	Data considerations	final issued
Data standards	Submission of data	final issued
Regulatory considerations	Applicability of regulations	final issued
Externally controlled trials	Design considerations	draft issued
Non-interventional studies	Design considerations	draft issued
RCTs in clinical practice settings	*Design considerations*	*in development*

https://www.fda.gov/science-research/real-world-evidence/center-biologics-evaluation-and-research-center-drug-evaluation-and-research-real-world-evidence

Non-Interventional Studies Guidance



Real-World Evidence: Considerations Regarding Non-Interventional Studies 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)
Oncology Center of Excellence (OCE)

March 2024
Real World Data/Real World Evidence (RWD/RWE)

Tala Fakhouri, PhD, MPH
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

REAGAN-UDALL FOUNDATION FOR THE FDA

Overview of Draft Guidance

Stefanie Kraus, JD, MPH
Senior Regulatory Counsel, Office of Regulatory Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

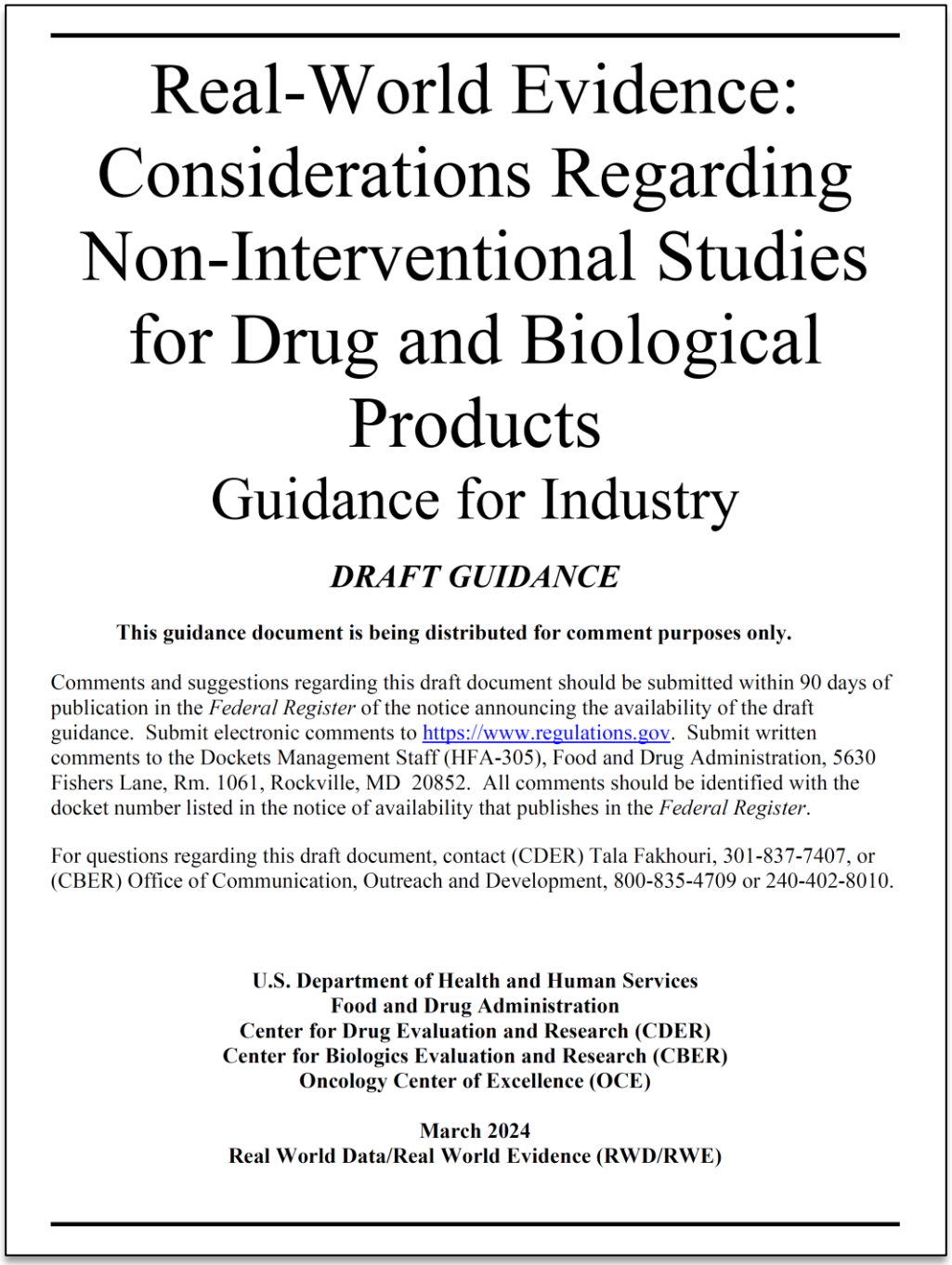
Public Webinar

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

30 May 2024

Tala Fakhouri, PhD, MPH
Associate Director for Policy Analysis
Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Stefanie Kraus, JD, MPH
Senior Regulatory Counsel
Office of Regulatory Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Real-World Evidence: Considerations Regarding Non-Interventional Studies 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)
Oncology Center of Excellence (OCE)

March 2024
Real World Data/Real World Evidence (RWD/RWE)

This Guidance:

- Focuses on non-interventional (observational) studies used to provide substantial evidence of effectiveness and/or evidence of safety of a drug

- Discusses attributes regarding the design and analysis of a non-interventional study that sponsors should consider when proposing a non-interventional study for such regulatory purposes

Definitions

- **Real-world data (RWD):** data relating to patient health status and/or delivery of health care routinely collected from a variety of sources
- **Real-world evidence (RWE):** clinical evidence about the usage and potential benefits/risks of a medical product derived from analysis of RWD
- **Non-interventional (observational) study**: a type of study in which patients receive the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol

Table of Contents

I. **INTRODUCTION**

II. **BACKGROUND**

III. **CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES**

- A. Overview
- B. Summary of the Proposed Approach
- C. Study Design
- D. Data Sources
- E. Analytic Approaches

Table of Contents

I. **INTRODUCTION**

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

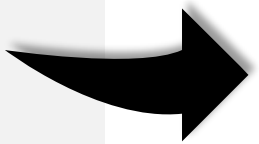
A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches



- Definition of non-interventional studies and examples of such studies
- How this guidance relates to other RWE guidances

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

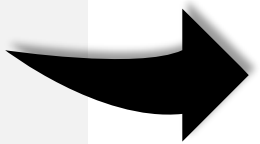
A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches



- Impact of confounding and other forms of bias on inferences from non-interventional studies

- Importance of identifying and addressing confounding and other forms of bias to be able to distinguish a true treatment effect from other influences

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview
B. Summary of the Proposed Approach
C. Study Design
D. Data Sources
E. Analytic Approaches

Meant to assist sponsors identifying and addressing commonly encountered challenges when using a non-interventional study for regulatory decision-making

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches

Overview

- Section III describes important attributes of a non-interventional study design and analysis
- FDA strongly encourages sponsors to engage with the Agency in the early stages of designing a non-interventional study
  - Detailed information may not be available or feasible to include at the time of early engagement with FDA
  - Successful proposals for non-interventional study designs should ultimately address each of the elements described in Section III

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches

Summary of the Proposed Approach

- Sponsors should finalize the study protocol before initiating study conduct
- Sponsors should briefly summarize alternative study approaches and candidate data sources they considered as well as discuss why alternative approaches were not feasible in answering the specific study questions (e.g., randomized trials, single-arm trials)
- Discussion should reflect an in-depth understanding of the proposed approach

Summary of the Proposed Approach (*continued*)

Sponsors should provide information on each of the study attributes listed below:

- Research question (study objective) and hypothesis
- Rationale for using the proposed non-interventional study design
- Choice of study design (e.g., cohort, case-control, self-controlled)
- Proposed selection of data sources to address the study objective and hypotheses, as well as alternative data sources considered

Summary of the Proposed Approach (*continued*)

Sponsors should provide information on each of the study attributes listed below:

- Results of any preliminary or feasibility studies conducted to assess which data source is fit for use to address the research question being posed and to estimate the statistical precision of a potential study without evaluating outcomes for treatment arms

- Proposed approach to support causal inference (e.g., target trial emulation or other conceptual approach) and to address confounding and other types of bias

- Description of how ethical considerations (e.g., issues related to human subject protection) are addressed

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches

Study Design

Based on the prespecified research question(s) identified, the sponsor should develop study design elements. Each protocol should concisely describe each of the critical elements listed below:

- Schema to describe overall study design as well as a causal diagram to specify the theorized causal relationship
- Source population (i.e., the population from which the study population will be drawn)
- Eligibility criteria and the study population (i.e., the population for which analyses will be conducted)
- Conceptual and operational definitions for key variables of interest and the status of validation efforts for operational definitions, as relevant

Study Design (*continued*)

Based on the prespecified research question(s) identified, the sponsor should develop study design elements. Each protocol should concisely describe each of the critical elements listed below:

- Relevant covariates (e.g., concomitant treatments) and corresponding strategies to address potential bias

- Index date (time zero) for all study arms and the approach to assigning an index date, including strategies to address potential bias introduced by issues related to immortal time

- Start and end of follow-up (at-risk) period, planned approach to censoring, and anticipated losses to follow-up (including depletion of susceptible patients)

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches

Data Sources

- Sponsors should demonstrate the appropriateness of the proposed data source(s) to address specific hypotheses and research questions

- Given that data sources used in a non-interventional study design are often generated for purposes other than research, it is important that sponsors understand the potential limitations of such data sources and determine whether those limitations can be addressed or if another data source should be pursued

Data Sources (*continued*)

Each protocol or accompanying documents should concisely describe each of the elements listed below:

- Description of the proposed data source(s), including how the data were originally collected
- Rationale for choosing the data source(s)
- Relevance of the data to the drug-outcome association of interest
- Appropriateness of the information on relevant confounding factors
- Available information on data reliability (including method of accrual from source data)

Data Sources (*continued*)

Each protocol or accompanying documents should concisely describe each of the elements listed below:

- Description of common data models used to provide a standard structure for sharing data from various sources and the rationale behind the choice of the specific model
- Available information on the timing of assessments for key data elements and completeness of these key data elements
- Explanation of how the proposed coding is appropriate based on operational definitions of key variables
- Appropriateness of the data relative to the target patient population

Data Sources (*continued*)

Each protocol or accompanying documents should concisely describe each of the elements listed below:

- Quality assurance activities that will be performed on the extracted original source data
- Existing or potential links to other data sources, as applicable (e.g., merging data from electronic health records and claims databases; linking an RWD source to a mortality database to confirm outcomes)
- Plans for additional data collection, as applicable

Table of Contents

I. INTRODUCTION

II. BACKGROUND

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview

B. Summary of the Proposed Approach

C. Study Design

D. Data Sources

E. Analytic Approaches

Analytic Approach

The prespecified Statistical Analysis Plan (SAP) should address the specific study objectives and detail the primary analysis and any secondary analyses. The plan should include information on each of the elements listed below:

- Assessment of feasibility, including sample size calculation and anticipated operating characteristics (e.g., statistical power)
- Statistical approach or method used to evaluate the treatment effect, including specification of the estimand (e.g., handling of intercurrent events and rules for censoring)
- Specific approach to account for potential confounding factors, including assessment of unmeasured confounding

Analytic Approach (*continued*)

The prespecified SAP should address the specific study objectives and detail the primary analysis and any secondary analyses. The plan should include information on each of the elements listed below:

- Evaluation of potential overadjustment of intermediate variables on the causal pathway
- Approach and rationale for subgroup analyses, as applicable
- Approach to address the potential for unequal detection of outcomes across compared groups (i.e., differential surveillance or differential misclassification)
- Approach to evaluate the potential for early manifestation of the outcome prompting the exposure (i.e., reverse causality)

Analytic Approach (*continued*)

The prespecified SAP should address the specific study objectives and detail the primary analysis and any secondary analyses. The plan should include information on each of the elements listed below:

- Approach to handling missing or misclassified data
- Approach to handling multiplicity (i.e., possible inflation of type I error due to multiple statistical tests, including analysis of multiple exposures or multiple outcomes)
- Description of planned sensitivity analyses, including details on which factors are proposed to be changed and rationale for such changes

Submitting Comments

- Submit either electronic or written comments on the draft guidance to Docket No. **FDA-2023-D-5470** by **June 18th, 2024**
- 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

Question and Answer

REAGAN-UDALL FOUNDATION FOR THE FDA

Moderated by

Susan C. Winckler, RPh, Esq.

Panelists

John Concato, MD, MS, MPH

Tala Fakhouri, PhD, MPH

Stefanie Kraus, JD, MPH

Next Steps

Submit comments on the draft guidance by June 18, 2024, to https://www.regulations.gov/docket/FDA-2023-D-5470 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

REAGAN-UDALL FOUNDATION FOR THE FDA

Thank you!