Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

The public meeting will begin shortly

Real-World Evidence Guidance Webinar Series

April 13, 2023 from 2-3 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 $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.

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2:10 pm	Overview of Draft Guidance
2:40 pm	Questions and Answer
2:55 pm	Closing Remarks
3 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)**

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Provide an overview and address questions from the public about the draft guidance titled *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*.

Submit comments on the draft guidance by May 2, 2023, to https://www.regulations.gov/docket/FDA-2022-D-2983 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

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

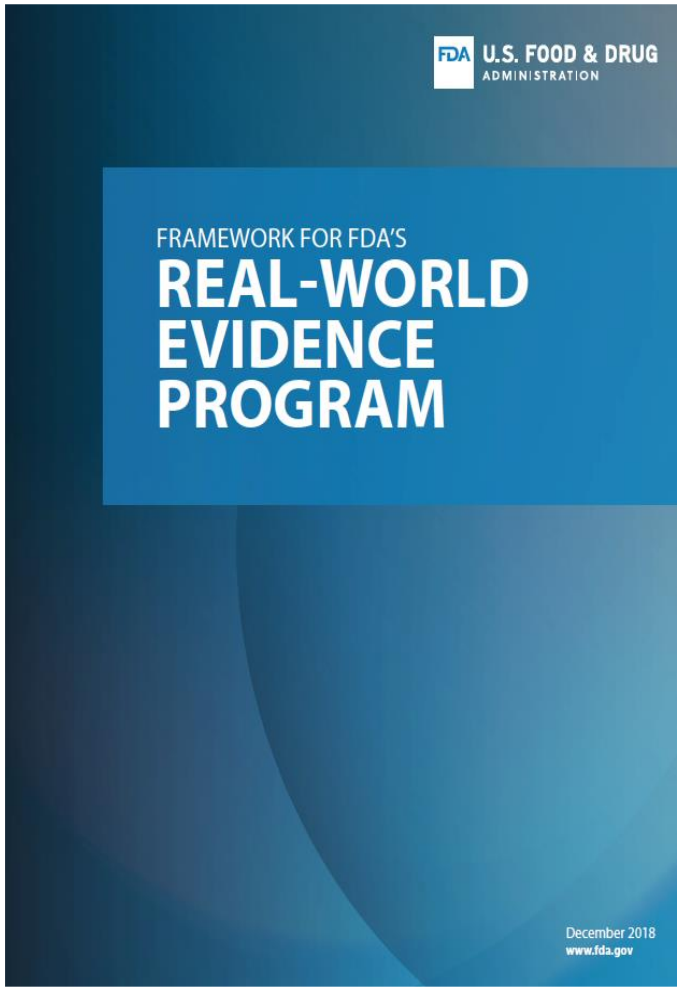
13 April 2023

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

- **FDA established a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support a new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework issued in December 2018**
- **Draft guidance for industry issued in Sep, Oct, Nov, Dec 2021; final guidance (on submitting documents w/ RWE) issued in Sep 2022**
- **Standard for substantial evidence remains unchanged; commitments met for Prescription Drug User Fee Act (PDUFA) VI; new Advancing RWE initiatives in PDUFA VII**

FDA's Framework and Program for Real-World Evidence



- **2018 *Framework* for FDA's Real-World Evidence (RWE) Program applies to Center for Drug Evaluation & Research (CDER), Center for Biologics Evaluation & Research (CBER), and Oncology Center of Excellence (OCE)**

- **Multifaceted program focused on RWE:**
  - **internal processes**
  - **external engagement**
  - **demonstration projects**
  - **guidance development**

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

Planned FDA Guidance – 2023

CDER Guidance Agenda
New & Revised Draft Guidance Documents
Planned for Publication in Calendar Year 2023[1]
(January 2023)

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

- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
- Considerations Regarding Non-Interventional Studies for Drug and Biological Products
- Using Clinical Practice Data in Randomized Controlled Trials (RCT) for Regulatory Decision-Making for Drug and Biological Products

[1] Final guidance documents planned for publication in calendar year 2023 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.

https://www.fda.gov/media/134778/download

Motiur Rahman, PhD, MS, MPharm
Senior Epidemiologist
Real-World Evidence Analytics
Office of Medical Policy
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REAGAN-UDALL FOUNDATION FOR THE FDA

Overview of Draft Guidance

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Supervisory Mathematical Statistician
Office of Translational Science
Office of Biostatistics
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Public Webinar

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

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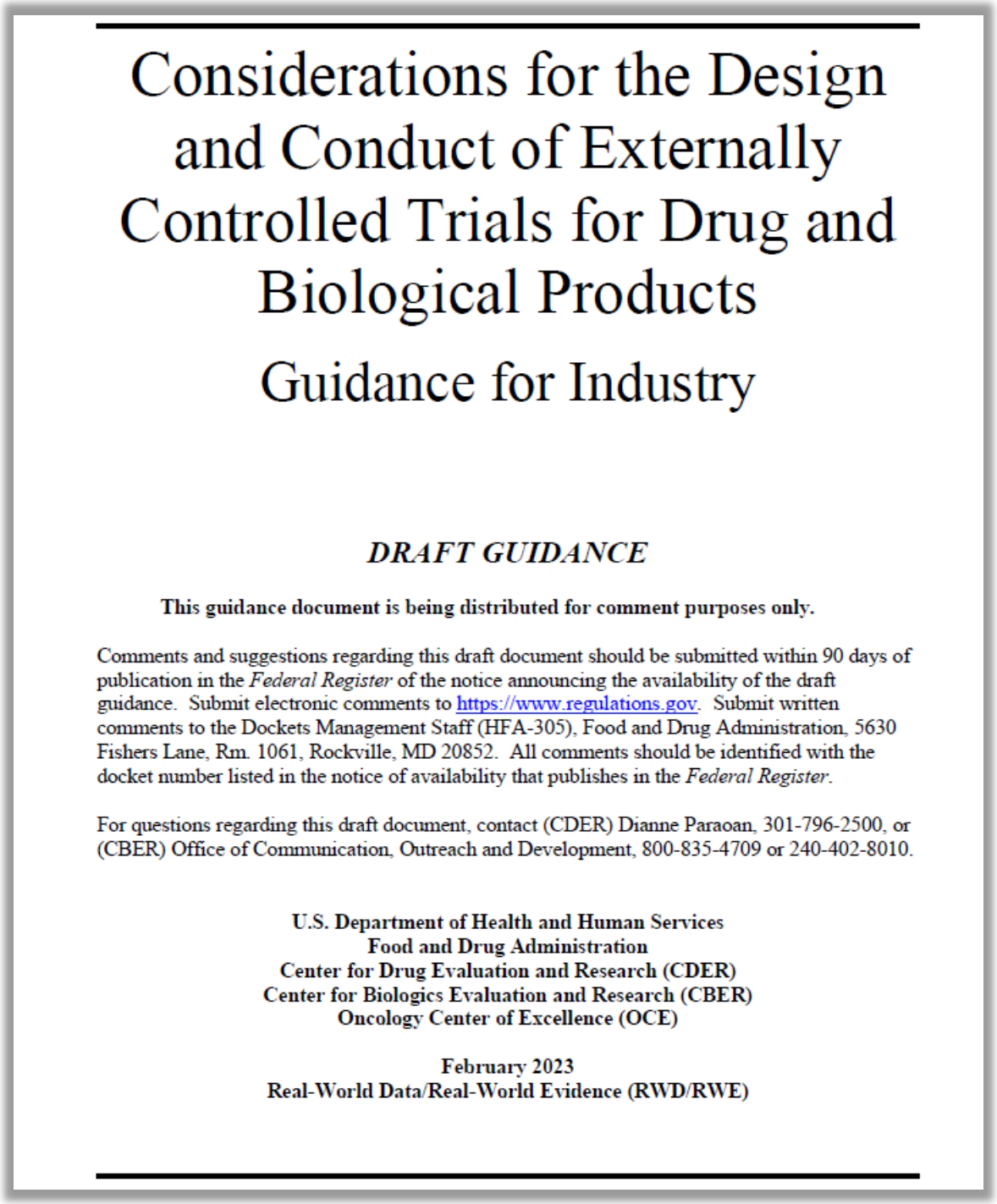

Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

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) Dianne Paraoan, 301-796-2500, 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)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

Focus of guidance:

- **Importance of design considerations (e.g., finalize protocol before analyzing data)**
- **Data considerations for the external control arm (e.g., various comparability issues)**
- **Analysis considerations (e.g., "FDA does not recommend a particular approach")**
- **Considerations to support regulatory review (e.g., access to patient-level data)**

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- Discusses types of external controls (e.g., historical or concurrent controls)
- Discusses suitability of such trials, and comparability of treatment and control arm populations
- Does not address external controls such as using summary-level estimates instead of patient-level data
- Does not discuss reliability and relevance of various sources of RWD

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Overview Section

- Sponsors should finalize a study protocol before initiating the externally controlled (EC) trial, including selection of the EC arm and analytic approach, rather than selecting an EC arm after the completion of a single-arm trial
- The estimand framework can be used to help design an EC trial
- Prespecify plans regarding how to measure and analyze data on important confounding factors and sources of bias:
  - Conceptually, a thorough understanding regarding the natural history of the disease and relevant prognostic factors is needed
  - From practical perspective, some confounding factors may be missing or measured differently in the EC arm compared to the treatment arm

Overview Section (cont'd)

- **An assessment of the extent of confounding and bias, along with analytic methods to reduce the impact of such bias, are critically important in the conduct of such trials**

- **EC trials are more likely to provide convincing results when the effect size on a well-characterized outcome of interest is anticipated to be large**

Characteristics of Study Population

- **Patient comparability: The population across both the trial arms should be as comparable as possible. Specific challenges can include –**
  - **Whether relevant confounding factors are known and well-characterized**
  - **Whether such confounding factors are captured and assessed appropriately**
  - **Whether the analytic methods sufficiently address differences across the groups**

- **Eligibility criteria: Protocol should include specific plans for evaluating eligibility criteria for selection of similar patients in both the groups**
  - **Unless a concurrent control group is used, sponsors should consider whether diagnostic criteria and relevant baseline factors have changed over time**

Attributes of Treatment

- **Potential imbalances: Unlike RCTs, important imbalances may occur between the trial arms involving factors related to the treatment of interest (e.g., adherence, dose, timing of initiation, and duration of treatment) and receipt of additional treatments**

- **EC arm derived from RWD: May lack detailed information on concomitant and supportive therapies, as well as the characteristics and administration of such therapies including drug formulation, dose, strength, route, timing, frequency & duration, specific rules for dose modifications, interruptions, or discontinuations**

Designation of Index Date (Time Zero)

- **Biased effect estimates:**
  - **Lack of randomization can lead to the differences in index date determination across trial arms which may lead to biased effect estimates**
  - **Any temporal differences in this date relative to treatment initiation or other important landmark times between treatment arms, especially when EC arm is derived from RWD sources, can bias the treatment effects**
- **Immortal time:**
  - **Determination of the index date in the treatment arm and the EC arm should avoid analyses that include a period of time (immortal time) during which the outcome of interest could not have occurred in one of the two arms**
  - **Failure to account for this bias may make the drug seem more effective than it actually is**

Assessment of Outcomes

- **Lack of blinding: Knowledge of the particular treatment by patients, caregivers, clinicians, or investigators can potentially lead to a biased treatment effect estimate**

- **Outcome ascertainment: Outcomes typically used in RCTs may be difficult to ascertain and evaluate in an RWD source. In general, outcomes are more likely to be recorded when events are objective and/or require immediate medical attention**

- **Timing of outcome assessment: In RWD, the timing and frequency of outcome assessments are determined during clinical care, whereas outcome assessments in the treatment arm are protocol-specified**

Assessment of Outcomes (cont'd)

- **Changes in diagnostic criteria: Can introduce bias when analyzing outcomes using a non-contemporaneous EC arm (or when using a reasonably contemporaneous EC arm that reflects a different diagnostic standard of care)**

- **Differential intercurrent events: In clinical trials, initiation of ancillary therapy after treatment with the drug of interest are protocol-determined, whereas RWD may not accurately capture additional therapies, potentially confounding the treatment effect**

- **Other considerations: Potential lack of standardization and training in the definitions and use of certain clinical outcomes assessments (COAs) in RWD compared to clinical trials settings can lead to bias in the measurements from an EC arm. Accordingly, COAs that are acceptable in RCTs may not be fit-for-use in EC trials**

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Data from Clinical Trials

- **Potential advantage over RWD: Comparability of populations could be established with respect to eligibility criteria, treatment administration, patterns of care, recording of concomitant medications, and outcome assessment**

- **Differential timing of data collection: May be of particular concern when the assessment and management of a disease changes over time, such as use of predictive or prognostic biomarkers in the patient population**

- **Other concerns: Bias could arise from the selection of an EC arm from a completed trial whose outcomes are already known, especially if the results of the EC arm are inconsistent with prior experience**

Data from RWD Sources

- **Data comparability: Establishing comparability of participant characteristics, timing and frequency of data collection, and patterns of care may be more challenging when when using RWD, as it is often collected for non-research purposes**

- **Missing information: Specific concerns regarding missing data from RWD sources can threaten the validity of the results of an EC trial. Moreover, insufficient information on relevant clinical characteristics (e.g., prognostic factors for the outcome of interest) may not allow for an appropriate comparison**

Considerations for Assessing Comparability of Data Across Trial Arms

- **Data comparability between the treatment and the EC trial arm should consider:**

  - Time periods
  - Geographic region
  - Diagnosis
  - Prognosis
  - Treatments
  - Other treatment-related factors
  - Follow-up periods
  - Intercurrent events
  - Outcomes
  - Missing data

- **The relevance of each consideration can vary on a case-by-case basis, depending on attributes of the treatment arm, the selected data source for the EC arm, and the stage of the trial (design, conduct, or analysis)**

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General Considerations

- Prespecified statistical analysis plan (SAP): Should be developed before conducting an EC trial, and should include primary analyses methods, sensitivity analysis plans and plans to control the chance of erroneous conclusions
- Analytic methods: No particular analysis method recommended; instead a justification, including strengths and limitations, for the methods should be provided
- Evaluation of comparability: Determining similarity across arms requires selection of population characteristics to compare, method for the comparison, and criteria to demonstrate similarity
- Effect size: When the anticipated effect size is modest, an EC trial may not be appropriate; should pre-specify analyses for confounders or other sources of bias

Missing Data

- Strategy for missing data: Include in the SAP a) reasons why data may not be available, b) characterization of patients with missing data, and c) sensitivity analyses to evaluate the impact of missing data on the primary analyses

- Missing data assumptions: Analytical methods (such as strategies for imputing missing data) may be used, but these methods require assumptions which may be unverifiable and/or difficult to justify

- Missing data due to intercurrent events: A special case of missing data; chosen estimand and corresponding SAP should account for these events, noting that some intercurrent events may not be captured in EC data sources, especially RWD

Misclassification of Available Data

- **Misclassification or mischaracterization can occur when the value of a measurement is assigned to an incorrect category for subsequent analysis, potentially affecting estimates of the observed drug-outcome association**
- **In RWD sources, different quantitative or qualitative descriptions of the same measure may be assigned to different categories by different healthcare providers**
- **Although analytical modeling methods could be used to assess the potential impact of misclassification, the best strategy to avoid bias is to use objective and reliable measurements for the data of interest**

Additional Analyses

- **Sponsors can use specific sensitivity analyses to test the vulnerability of trial results to assumptions in the analysis plan**
- **Prespecified supplementary analyses can provide further understanding of the treatment effect**

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Communication with FDA

- **Early engagement: Sponsors should consult with the relevant FDA review division early in a drug development program about whether it is reasonable to conduct an EC trial instead of an RCT. Sponsors should provide a detailed description of:**
  - **Reasons why the proposed study design is appropriate**
  - **Proposed data sources for the EC arm and an explanation of fitness for use**
  - **Planned statistical analyses**
  - **Plans to address FDA's expectations for the submission of data**

Access to Data and Documents

- **Sponsors must include in their marketing applications relevant patient-level data, as required under FDA regulations, for both the treatment and EC arms**
- **If sponsors do not own the data used for the EC arm, they should structure their agreements with the data owners to ensure that patient-level data can be provided to FDA**

Submitting Comments

- **Submit either electronic or written comments on the draft guidance to Docket No. FDA-2022-D-2983 by May 2, 2023**
- **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

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Moderated by

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Pallavi Mishra-Kalyani, PhD

Next Steps

Submit comments on the draft guidance by May 2, 2023, to https://www.regulations.gov/docket/FDA-2022-D-2983 to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance

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Thank you!