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

## *Draft Guidance for Industry*

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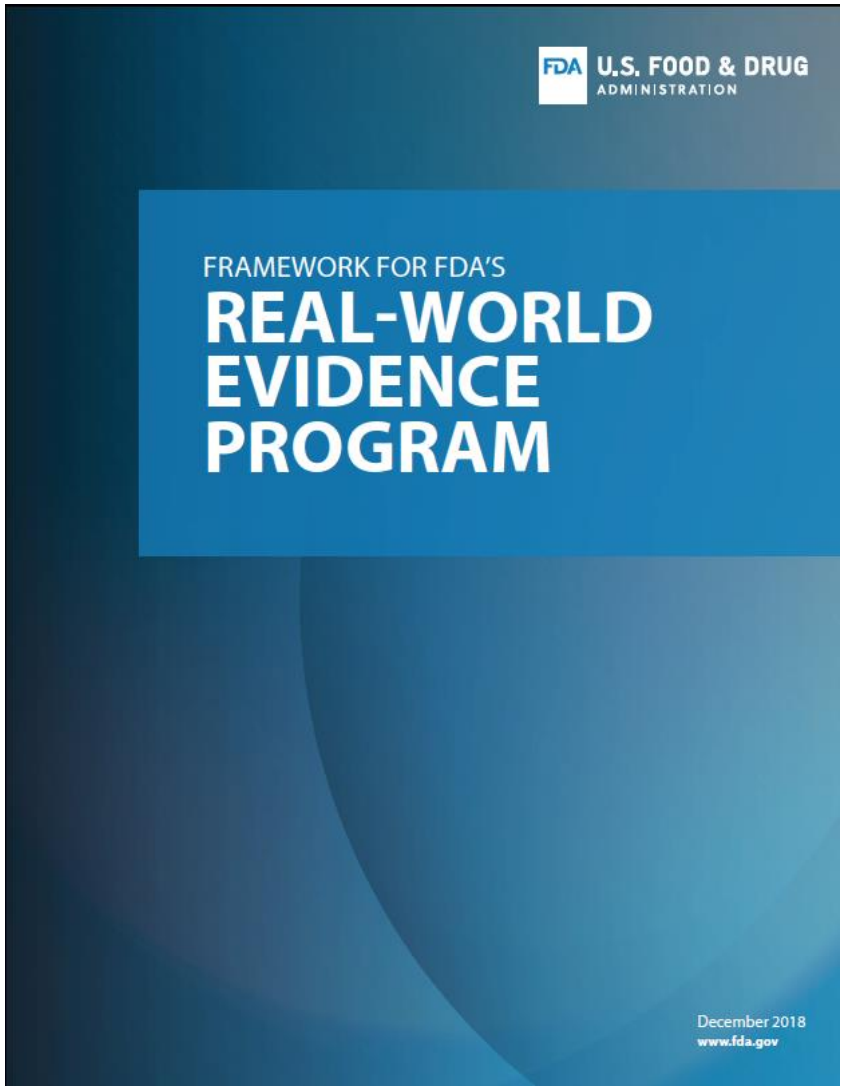
# Regulatory Guidance and Resources

- December 2018: FDA provided the Framework for the Real-World Evidence Program[2], includes information on how RWD/RWE will be incorporated into regulatory decision making

- Applies to Center for Drug Evaluation & Research (CDER), Center for Biologics Evaluation & Research (CBER), and Oncology Center of Excellence (OCE)
  - Does not apply to Center for Devices & Radiological Health (CDRH)




[1] https://www.fda.gov/downloads/guidances/ucm073139.pdf
[2] https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

# Regulatory Guidance & Resources

FDA has published several draft Guidances related to Real-World Data and Real-World Evidence[1]:

- Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
- Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
- 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
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
- Use of Electronic Health Records in Clinical Investigations
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices



[1] https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence

# External Controls Guidance

## 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***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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)**

**TABLE OF CONTENTS**





https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

# External Controls Guidance

- Draft Guidance for Industry published February 2023
- Sections I and II of the guidance provide an introduction and important background information, including the parameters of what the guidance does and does not address
  - 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
- Section IV provides considerations to support regulatory review (such as access to patient-level data)



[1]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

# External Controls Guidance

- Section III of the Guidance provides key considerations for design and analysis of EC Trials
  - **Design considerations**
    - Protocol should be finalized before initiating the externally controlled (EC) trial
    - Can consider estimand framework to aid design (and analysis plan)
    - Prespecify plans for measuring and analyzing on confounding factors and sources of bias
  - **Data selection** for the external control arm, including a comprehensive table describing comparability considerations
  - **Analysis plan** should be prespecified, thorough (sensitivity analyses, missing data plans, etc), and include a formal evaluation of comparability



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# Data Comparability

| Focus of Comparison | Considerations for Data Comparability |
|---|---|
| Time periods | Various aspects of clinical care may change over time, such as the standard of care for the condition of interest, types of treatments, supportive care regimens, and criteria for determining disease response or progression. Such temporal differences are difficult to address using statistical analyses alone. It is important to consider whether and how different time frames in the treatment arm and the external control arm impact the interpretability of study findings. |
| Geographic region | Standards of care and other factors (e.g., access to care) that affect health-related outcomes can vary across geographic regions and health care systems. A balance of participants or patients across geographic regions and health care systems in an externally controlled trial, when possible, can help reduce the impact of confounding based on such differences. |
| Diagnosis | The criteria used to establish a diagnosis may differ based on practice variation or may have changed in the interval between when the treatment arm of the trial was conducted and when the data for the external control arm were collected. Sponsors should consider the diagnostic standards used and whether relevant clinical tests to establish a diagnosis were conducted and reported equally across the compared arms. |
| Prognosis | Based on demographic and clinical characteristics—and if sufficient knowledge of relevant prognostic factors is available—prognostic indicators for the participants or patients in each arm of the trial should be evaluated and shown to be of sufficient similarity to permit an unbiased assessment of the treatment-outcome association. |
| Treatments | Attributes of the treatment of interest—including drug formulation, dose, route of administration, timing, frequency, and duration as well as specific rules for dose modifications, interruptions, discontinuations, and adherence—will have been prespecified or measured in the treatment arm. In contrast, specific aspects of a comparator treatment (as applicable) in the external control arm may not have been protocol-driven depending on the data source. Accordingly, sponsors should assess whether the external control arm data can be meaningfully compared to the treatment arm data. |

| Focus of Comparison | Considerations for Data Comparability |
|---|---|
| Other treatment-related factors | Various treatment-related considerations, when relevant, include (1) previous treatments received (e.g., lines of therapy in patients with cancer), (2) medications received concomitantly that can affect the outcome of interest, or (3) predictive biomarkers (e.g., genomic testing) related to the treatment of interest. When differentially distributed across groups being compared, such factors can threaten an assessment of the drug-outcome association. |
| Follow-up periods | Designation of the index date should be consistent between the treatment arm and the external control arm, and the duration of follow-up periods should be comparable across compared arms. |
| Intercurrent events | The relevance of intercurrent events across treatment arms should be assessed, including differential use of additional therapies after initiation of the treatment of interest. |
| Outcome | Whether endpoints used in an externally controlled trial can be reliably and consistently measured across the external control arm and the treatment arm will be influenced by several factors, including the definitions of the endpoints, the data source for the external control arm, and the potential for the outcome to be influenced by knowledge of treatment received. In addition, sponsors should be able to apply the same criteria for the evaluation and timing of outcome assessments across both arms of the externally controlled trial. |
| Missing data | The extent of missing data in the external control arm should be assessed before conducting an externally controlled trial to evaluate feasibility (when such data are available). When analyzing results from such a trial, the extent of missing data in both the treatment and external control arms should be assessed to examine the potential impact of missing data. |



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# Acknowledgements and Next Steps

- Guidance is a joint effort, lead by FDA CDER. Individuals from the following Offices (from CDER) and Centers contributed:
  - 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

- Public comment period has concluded on May 2, 2023
  - FDA will consider submitted comments while editing and reissuing as final guidance



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