

Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development

Virtual Public Workshop

June 7-8, 2023

Resource Guide

Event Background and Objectives

Although the Orphan Drug Act defines a rare disease as a disease or condition that affects less than 200,000 people in the United States, collectively these conditions impact an estimated 30 million people in the United States. Significant unmet treatment needs remain for many of those living with one of the 7,000 – 10,000 known rare diseases. Advancing the development of treatments for these individuals is critical, as many rare diseases are progressive, considered serious or life-threatening, and nearly half affect children. However, traditional clinical trials are challenging to conduct for therapies targeting small populations. Additionally, many rare disease communities have significant heterogeneity of disease presentation or poorly characterized natural history, further complicating clinical trials for products in the rare disease space. Well-developed efficacy endpoints, especially those that could apply to other rare diseases with similar manifestations, can help drive the general advancement of rare disease drug development.

In order to facilitate rare disease drug development, and as part of a performance goal and requirement related to the FDA User Fee Reauthorization Act of 2022 and the Food and Drug Omnibus Reform Act of 2022 (FDORA), respectively, the U.S. Food and Drug Administration (FDA) has established a pilot program for supporting the development of efficacy endpoints for rare disease treatments. The new Rare Disease Endpoint Advancement (RDEA) Pilot Program offers additional engagement opportunities with the FDA to sponsors of rare disease development programs that meet specific criteria. The PDUFA [Prescription Drug User Fee Act] Reauthorization Performance Goals and Procedures Fiscal Years 2023-2027, known as the PDUFA VII Commitment Letter, contains detailed requirements for participating in the program and outlines the FDA's commitment to conduct up to three public workshops by the end of fiscal year 2027 to discuss topics relevant to endpoint development for rare diseases. In addition, FDORA requires the conduct of up to three public workshops to discuss topics relevant to the development of endpoints for rare diseases by September 30, 2026. This public workshop is intended to meet a performance goal under PDUFA VII and a requirement under FDORA.

The Duke-Margolis Center for Health Policy, under a cooperative agreement with the FDA, is convening this two-day event that will illustrate challenges and opportunities in rare disease endpoint development, introduce attendees to the RDEA Pilot Program, and highlight how the RDEA Pilot Program is structured to support sponsors who may encounter challenges with endpoint development. Attendees will hear from a variety of speakers about rare disease endpoint development examples to gain a better understanding of endpoint development challenges and opportunities. Workshop programming will also facilitate a shared understanding of the RDEA Pilot Program's purpose and structure, including key features of the program such as sponsor disclosure requirements. Learnings from other FDA pilot programs that share programmatic features with the new RDEA Pilot Program will also be discussed. This event is intended to serve as a resource for sponsors and other attendees interested in learning how they might engage with the FDA through this new program.

This document contains information pertaining to the June 2023 virtual public event and key resources for attendees interested in rare disease endpoint development.

Event Logistics and Important Dates

This virtual public event will take place on Wednesday, June 7 and Thursday, June 8, 2023, from 1:00 to 5:00 pm ET. The event registration and additional details can be found [here](#). Please note that this event will be recorded, and the recording will be made available on the Duke-Margolis website. Workshop materials and the workshop recording will be added to this webpage as they become available.

Stakeholders may submit written comments regarding this event to [regulations.gov](https://www.regulations.gov) until July 23, 2023. For further information on submitting comments for the workshop, please visit [Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development; Public Workshop; Request for Comments](#). Comments in the docket will be reviewed after the docket closes.

About the RDEA Pilot Program

The RDEA Pilot Program is an FDA pilot meeting program intended to support the goal of advancing and facilitating the development and timely approval of drugs and biological products for rare diseases, including rare diseases in children. In connection with PDUFA VII, FDA committed to establishing a pilot meeting program for the development of novel efficacy endpoints in rare disease drug development programs for: (1) sponsors with an active investigational new drug (IND) or pre-IND for the rare disease or a development program for a common disease that includes innovative or novel endpoint elements if there is sufficient justification that the endpoint could be applicable to a rare disease; or (2) sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied.

This pilot program will offer sponsors of selected proposals an opportunity for increased engagement with FDA experts from the Center for Drug Evaluation and Research (CDER) and/or Center for Biologics Evaluation and Research (CBER) to discuss novel efficacy endpoints intended to establish substantial evidence of effectiveness for a rare disease treatment. The RDEA Pilot Program commenced October 1, 2022, and will proceed through September 30, 2027. Sponsors may submit RDEA program proposals beginning July 1, 2023, through June 30, 2027.

Compiled below are references and resources that provide additional information about the RDEA Pilot Program.

RDEA Pilot Program References and Resources:

- [RDEA Pilot Program Webpage](#)
This webpage provides information about the RDEA Pilot Program's goals, general program and submission information, eligibility criteria, proposal selection, and frequently asked questions.
- [RDEA FAQs](#) (accessible from RDEA pilot program webpage)
This webpage provides answers to frequently asked questions about the RDEA Pilot Program.
- [RDEA Pilot Program FRN announcement](#) (published Oct 27, 2022)

The FRN announcement provides a summary of the RDEA Pilot Program along with important information about timelines and the goals of early meeting discussions granted under this program.

- [PDUFA VII commitment letter](#) (see pages 29-34)
This document details the performance goals and procedures for the Prescription Drug User Fee Act (PDUFA) reauthorization for fiscal years (FYs) 2023-2027, known as PDUFA VII.

Pages 29-34 provide information about the RDEA Pilot Program, including its scope, process and timeline, and commitment to transparency and endpoint advancement.

- [FDORA \(the Food and Drug Omnibus Reform Act\)](#)
FDORA is a subsection of the Consolidated Appropriations Act, 2023. Section 3208 concerns the RDEA Pilot Program.

About Rare Disease Endpoint Development

Endpoints are typically direct or indirect measures of clinical benefit for clinical trials intended to evaluate the efficacy and safety of a new medical product or a new use of an approved product. Investigators typically use either clinical or surrogate endpoints for the purposes of these clinical trials. This event will focus on rare disease endpoint development challenges and opportunities to discuss four types of endpoints, based on the tools the endpoints use or their key features: biomarkers, digital health technologies (DHT), clinical outcome assessments (COAs), and multiple endpoints.

Biomarkers and Surrogate Endpoints

The Biomarkers, EndpointS and other Tools (BEST) glossary defines a biomarker as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics may contribute to a biomarker. A biomarker is not a direct measure of clinical benefit, as it is not an assessment of how an individual feels, functions, or survives.”¹

Biomarkers can be qualified through a formal process by the FDA for use in drug development and regulatory review. Qualified biomarkers may be beneficial in the regulatory review process by reducing uncertainty in regulatory decision-making.²

Relevant FDA resources:

- [Biomarker Qualification Program](#) (webpage)
The Biomarker Qualification Program works with external stakeholders to develop biomarkers as drug development tools.
- [Surrogate Endpoint Resources for Drug and Biologic Development](#) (webpage)
This webpage collates resources related to the use of surrogate endpoints in drug and biologic development.

- [Considerations for Discussion of a New Surrogate Endpoint\(s\) at a Type C PDUFA Meeting Request \(document\)](#)

This document provides details and guiding questions for sponsors planning to use novel surrogate endpoints (SEs) as primary efficacy endpoints to engage with FDA.

Digital Health Technology

DHTs have been defined by FDA as “system[s] that use computing platforms, connectivity, software, and/or sensors, for healthcare and related uses.”³ There are many types of DHTs available for application in clinical research, including some which meet the definition of a device under the Federal Food, Drug, and Cosmetic Act. DHTs may take the form of hardware and/or software, and DHT software may run on general-purpose computing platforms (e.g., mobile phone, tablet, or smart watch). Clinical investigations may use multiple DHTs to collect a range of information, including clinical, physiological, psychological, behavioral, or functional data.⁴

FDA guidance on DHTs notes that “DHTs used for remote data acquisition are playing a growing role in health care and offer important opportunities in clinical research.” Use of DHTs allows for researchers to collect data from trial participants more frequently or even continuously. This approach to data collection may provide a broader picture of how participants feel or function in their daily lives, as DHTs can record data directly from trial participants (e.g., performance of activities of daily living, sleep) wherever the participants may be (e.g., home, school, work, outdoors). Some DHTs may facilitate data collection from trial participants who are unable to report their experiences (e.g., infants, cognitively impaired individuals).⁴

Relevant FDA resources:

- [Digital Health Technologies for Remote Data Acquisition in Clinical Investigations \(draft guidance\)](#)

This guidance outlines recommendations intended to facilitate use of DHTs in a clinical investigation as appropriate for the evaluation of medical products.

These recommendations address some of the information that should be contained in an IND or IDE [investigational device exemption] application for a clinical investigation in which the sponsor plans to use one or more DHTs or in a marketing application that includes such a clinical investigation.

Clinical Outcome Assessment

FDA has defined COA as “a measure that describes or reflects how a patient feels, functions, or survives.”⁵ Types of COAs include patient-reported outcome (PRO) measures, observer-reported outcome (ObsRO) measures, clinician-reported outcome (ClinRO) measures, and performance outcome (PerFO) measures. COAs may be qualified voluntarily for use in drug development.

FDA has provided information surrounding the use of COAs in regulatory decision-making: “For regulatory purposes, high-quality information from COAs can provide valuable evidence for benefit-risk assessments. They can also be used in medical device labeling to communicate the effect of a treatment on patient symptoms and functioning. COAs may be used to determine who is eligible for a clinical study and measure how well the device performs in treating or diagnosing the condition. COAs may also be used to help measure the safety of the device.”⁵

Relevant FDA resources:

- [Clinical Outcome Assessment \(COA\) Qualification Program](#) (webpage)
The COA Qualification program manages the qualification process for COAs intended to address unmet public health needs and works directly with requestors in guiding COA development for qualification.

The program also provides a setting where CDER can review COAs and provide advice on the development or modification of COAs outside the IND/NDA/BLA pathway.
- [Clinical Outcome Assessment Compendium](#) (webpage)
The COA Compendium is a part of FDA's efforts to foster patient-focused drug development.

The COA Compendium intends to facilitate communication and provide clarity and transparency to drug developers and researchers by collating and summarizing COA information for many different diseases and conditions into a single resource.

The COA Compendium can be used as a starting point when considering a COA for use in clinical trials.
- [Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments \(PFDD Guidance 3, draft\)](#)
Guidance 3 discusses approaches to selecting, modifying, developing, and validating COAs to measure outcomes of importance to patients in clinical trials.
- [Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making \(PFDD Guidance 4, draft\)](#)
Guidance 4 addresses methodologies, standards, and technologies that may be used for the collection, capture, storage, and analysis of COA data. The guidance also addresses methods to better incorporate COAs into endpoints that are considered significantly robust for regulatory decision-making. This includes methods to define meaningful change in a COA-based endpoint and interpretation of results. The guidance includes information on the format and content required for regulatory submissions incorporating patient experience, COA data.

Multiple Endpoints

Clinical trials in drug development typically contain multiple endpoints to assess the effects of the drug and to document the ability of the drug to favorably affect one or more disease characteristics. Most diseases can lead to multiple clinical events, symptoms, and/or altered functions, so clinical trials may be designed to examine the effect of a drug on more than one aspect of the disease. FDA guidance has advised that efficacy cannot be adequately established based on a single disease aspect in some cases, so studies should use either an endpoint that incorporates multiple aspects of the disease into a single endpoint or effects should be demonstrated on multiple endpoints. However, in other cases, an effect on any of several endpoints may be sufficient to support approval of a marketing application.⁶

FDA guidance has articulated challenges that multiple endpoints may present, noting, “When more than one endpoint is analyzed in a single trial, the likelihood of making false conclusions about a drug’s effects with respect to one or more of those endpoints could increase if there is no appropriate adjustment for multiplicity.”⁶

Relevant FDA resources:

- [Multiple Endpoints in Clinical Trials \(final guidance\)](#)
This guidance provides the Agency’s thinking about the problems posed by multiple endpoints in the analysis and interpretation of study results, and how these problems can be managed in clinical trials for human drugs.

This guidance describes various strategies for grouping and ordering endpoints for analysis and applying statistical methods for controlling the chance of making erroneous conclusions about a drug’s effects.
- [Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making \(PFDD Guidance 4, draft; see COA section above\)](#)

Additional Resources

Rare Disease Drug Development Resources:

- [Rare Diseases: Common Issues in Drug Development \(draft guidance\)](#)
The purpose of this guidance is to assist sponsors of drug and biological products for the treatment or prevention of rare diseases in conducting more efficient and successful drug development programs.
- [Rare Diseases: Natural History Studies for Drug Development \(draft guidance\)](#)
This guidance is intended to help inform the design and implementation of natural history studies that can be used to support the development of safe and effective drugs and biological products for rare diseases.
- [Human Gene Therapy for Rare Diseases \(final guidance\)](#)
This guidance provides recommendations to sponsors developing human gene therapy products intended to treat a rare disease in adult and/or pediatric patients regarding the manufacturing, preclinical, and clinical trial design issues for all phases of the clinical development program.

Patient-Focused Drug Development Resources:

- [FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient’s Voice in Medical Product Development and Regulatory Decision Making](#)
(webpage also has links to recordings, transcripts, recordings for PFDD guidance workshops)

The FDA is developing a series of four methodological patient-focused drug development (PFDD) guidance documents that describe how stakeholders such as patients, caregivers, researchers, and medical product developers can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-making.

This webpage contains information related to FDA's development of the methodological PFDD guidances, including public workshops, draft guidances, and hypothetical scenarios.

- [Patient-Focused Drug Development: Collecting Comprehensive and Representative Input \(PFDD Guidance 1, final\)](#)
Guidance 1 discusses methods to collect patient experience data that are accurate and representative of the intended patient population.
- [Patient-Focused Drug Development: Methods to Identify What Is Important to Patients \(PFDD Guidance 2, final\)](#)
Guidance 2 discusses approaches to identifying what is most important to patients with respect to their experience as it relates to burden of disease/condition and burden of treatment.
- [Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments \(PFDD Guidance 3, draft; see COA section above\)](#)
- [Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making \(PFDD Guidance 4, draft; see COA section above\)](#)

Other General Resources:

- [BEST Resource Taxonomy](#) (webpage)
The Biomarkers, Endpoints, and other Tools (BEST) glossary clarifies important definitions and hierarchical relationships among terms related to study endpoints and biomarkers.
- [Qualification Process for Drug Development Tools \(final guidance\)](#)
This guidance represents CDER's and CBER's current thinking on implementation of Section 507 of the Federal Food, Drug, and Cosmetic Act with respect to describing the process for requestors interested in qualifying drug development tools (DDTs) and on taxonomy for biomarkers and other DDTs.
- [E9\(R1\) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials \(final guidance\)](#)
This addendum presents a structured framework to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect or effects of interest that a clinical trial should address.

FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

References

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