On The RISE: Controls in Rare Disease Clinical Trials for Small and Diminishing Populations

September 3, 2025

9:30 am – 4:00 pm ET

Hybrid Public Meeting | National Press Club

Meeting Background and Objectives:

Adequate and well-controlled clinical investigations provide the basis for determining whether there is substantial evidence to support claims of effectiveness in new drug approvals. However, conducting these clinical trials in small and diminishing populations poses unique challenges. While regulatory guidance on the topic exists and approvals of drugs and biologics to treat patients with rare diseases have increased, ethical, scientific, and practical questions persist, warranting further discussion around existing options and the role of innovative control options in this population.

This public workshop, convened by the Duke-Margolis Institute for Health Policy under a cooperative agreement with the U.S. Food and Drug Administration (FDA), will explore considerations when choosing a control, discuss existing and innovative control options internal and external to the trial, and identify how these controls can be used to generate evidence that supports regulatory decision-making. This workshop assumes a working knowledge of FDA guidance documents for rare disease drug development, including Considerations for the Development of Drugs and Biological Products, Natural History Studies for Drug Development, and Human Gene Therapy for Rare Diseases. Meeting participants will discuss considerations, current challenges, and potential uses of controls and identify areas of consideration for the FDA's Rare Disease Innovation Hub.

Agenda

9:30 am **Welcome**

Gerrit Hamre, Duke-Margolis Institute for Health Policy

9:35 am **Opening Remarks**

Amy Comstock Rick, RDIH, U.S. Food and Drug Administration
Vinay Prasad, CBER, U.S. Food and Drug Administration (Virtual)
George Tidmarsh, CDER, U.S. Food and Drug Administration (Virtual)

10:00 am **Session 1: Considerations for Control Decisions**

Designing and conducting trials can be challenging in the setting of rare diseases with small and heterogeneous disease populations. This session will explore considerations for determining the appropriate choice of a control and if a control is

needed, including ethical, scientific, and practical factors, in the setting of rare diseases.

Moderator: **Gerrit Hamre**, Duke-Margolis Institute for Health Policy

Panelists*:*

Stacey Frisk, Rare Disease Company Coalition
Cara O'Neill, Cure Sanfilippo Foundation
Marshall Summar, Uncommon Cures, LLC
Karmen Trzupek, Global Genes

Moderated Discussion and Q&A

11:00 am **Break**

11:15 am **Session 2: Internal Control Options**

Building on the previous session, this session explores controls internal to the trial, such as active controls, crossover designs, baseline controlled trials, and master protocols. Participants will highlight considerations, current challenges, and potential uses for internal controls. The session will conclude with a panel discussion.

Moderator: **Rachel Sher**, Manatt, Phelps & Phillips, LLP

Presentations:

Todd Paporello, Sanofi

Additional Panelists:

Allyson Berent, Foundation for Angelman Syndrome Therapeutics
Rebecca Rothwell Chiu, CDER, U.S. Food and Drug Administration
Jenn McNary, Patient Advocate, Canary Advisors, LLC
Adora Ndu, BridgeBio
Tingting Zhou, CBER, U.S. Food and Drug Administration

Moderated Discussion and Q&A

12:30 pm **Lunch Break**

1:45 pm **Session 3: External Control Options**

In this session, participants will discuss options for controls external to the trial in addition to approaches on the horizon. A variety of approaches will be discussed, including using data from natural history studies, historical controls, and utilizing Bayesian statistical methods.

Moderator: **Rachele Hendricks-Sturrup**, Duke-Margolis Institute for Health Policy

Presentations:

Ramona Belfiore-Oshan, Critical Path Institute (C-Path)
Nicole Mayer Hamblett, Cystic Fibrosis Therapeutics Development Network

Additional Panelists:

Najat Bouchkouj, CBER, U.S. Food and Drug Administration
Scott Demarest, Children's Hospital Colorado
Tracey Sikora, National Organization for Rare Disorders (NORD)
Arup Sinha, CDER, U.S. Food and Drug Administration

Moderated Discussion and Q&A

3:00 pm **Break**

3:15 pm **Session 4: Where do we go from here?**

Panelists will discuss the main takeaways from the day and how this can inform the Rare Disease Innovation Hub's continued efforts. The session will conclude with an opportunity for feedback from the audience and ideas on optimizing control strategies for clinical trials in small and diminishing patient populations.

Moderator: **Steve Berman**, Biotechnology Innovation Organization (BIO)

Panelists:

Samiah Al-Zaidy, Alexion
Elizabeth Berry-Kravis, Rush University
Mary Dwight, Cystic Fibrosis Foundation
Annie Kennedy, EveryLife Foundation for Rare Diseases
Vijay Kumar, CBER, U.S. Food and Drug Administration
Mark Levenson, CDER, U.S. Food and Drug Administration

Moderated Discussion and Q&A

3:55 pm **Concluding Remarks**

Gerrit Hamre, Duke-Margolis Institute for Health Policy

4:00 pm **Adjournment**

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