# 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

## Workshop Summary

### Background

In 2024, the U.S. Food and Drug Administration (FDA or Agency) created the Rare Disease Innovation Hub (RDIH or the Hub), which brings together experts from the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) to advance cross-disciplinary approaches related to rare disease product review and promote consistency in regulatory approach across offices and Centers. The Hub's mission is to promote collaboration across the FDA, advance a shared vision to address common challenges in the rare disease space, identify and utilize innovative scientific approaches to drug development, and streamline communications with the rare disease community.[1]

The Duke-Margolis Institute for Health Policy, under a cooperative agreement with the FDA, convened a hybrid public workshop in partnership with the Hub entitled "On the RISE: Controls in Rare Disease Clinical Trials for Small and Diminishing Populations." This meeting, held on September 3, 2025, convened regulators, patients, advocacy organizations, pharmaceutical industry representatives, clinicians, and researchers to discuss considerations when choosing a control in the context of small and diminishing rare disease populations. Discussion throughout the day explored existing and innovative control options internal and external to the trial, and how these controls can be used to generate evidence that supports regulatory decision-making.

This workshop is the first in a series of Rare Disease Innovation, Science, and Exploration (RISE) public workshops to be hosted by the RDIH, with the second workshop set to occur in November 2025. These workshops aim to inform the future efforts of the Hub and provide an opportunity for public engagement and joint solutioning concerning rare disease-related topics.

While adequate and well-controlled trials serve as the standard for supporting substantial evidence and effectiveness for new drug approvals, small and diminishing populations pose unique challenges to conducting clinical trials. Despite the existence of regulatory guidance and increasing approvals of drugs and biologics to treat rare diseases, ethical, scientific, and practical questions remain. In this public workshop, participants discussed the challenges that exist in rare disease

[1] Rare Disease Innovation Hub | Strategic Agenda 2025

settings with small and diminishing populations and envisioned a way forward that encompassed multi-sectoral considerations.

## Key takeaways from the day included:

- **Sharing data** has a critical role in furthering product development for rare diseases. Participants emphasized the need for developers, patient organizations, and other stakeholders to share de-identified data to address some of the challenges that small, heterogeneous populations present in clinical trials.
- **Identifying endpoints** that are well defined, clinically meaningful, and have a well understood biological effect, while also aligning with what is meaningful to the patient, is necessary. This can best be accomplished by bringing patients into the trial design as early as needed to help identify target endpoints.
- **Disease archetypes** could provide better starting points for patients and sponsors when selecting a control. Learning from diseases that share similarities in symptoms and symptom progression was identified as particularly advantageous for designing trials in rare diseases.
- **Collaboration and alignment** on endpoints, trial designs, and methods between all stakeholders (e.g., sponsors, regulators, and patients) is essential and can be achieved through more transparent, early, and regular communication.
- **Well-developed natural history studies, registries, innovative statistical methods, and trial designs** are crucial to the success of clinical trials and reducing patient burden in small and diminishing populations.

## FDA Initiatives Promoting Regulatory Flexibility

The workshop began with remarks from the Directors of the CBER, CDER, and the RDIH. Remarks from the CBER Director emphasized their commitment to support flexibility in drug development for rare diseases and used immunotherapy AAV as an example of how the agency can show flexibility. A balance should be struck between ensuring safety and allowing available treatments to reach the market to benefit small and diminishing patient populations. Building off these remarks, CDER's Director highlighted the strong foundation that exists for rare disease drug review. In an effort to further these goals, he announced the CDER/CBER Rare Disease Evidence Principles (RDEP), a new process to facilitate the approval of drugs to treat rare diseases with a known genetic defect as the major driver of pathophysiology. The RDIH Director rounded out the opening session by sharing that the vision of the RISE workshop series is to address challenges that persist among multiple diseases or a disease class and for which evolving science offers innovative solutions for treatment development.

## Navigating Control Decisions for Small Populations

This first session began with initial remarks from the patient, researcher, and industry perspectives on the challenges for designing and conducting trials for rare diseases with a small and

heterogeneous disease population before diving into a deeper discussion. All panelists spoke to the need for flexible approaches to trial design, citing the advancements in technology, statistical methodology, and biological understanding that can make these approaches scientifically rigorous, ethically sound, and more feasible. Fit-for-purpose alternatives such as adaptive designs and external controls (including natural history studies) could address some of the challenges, such as heterogeneity of the patient population and small patient population, and may be better at demonstrating safety and efficacy.

When conducting clinical trials in these rare disease populations, panelists voiced the need to consider the small patient pool. As science advances, more rare diseases are identified and/or patients within the same rare diseases are further stratified based on genetic differences, thus further shrinking the patient pools for these diseases. Randomized placebo-controlled trials, which are often referred to as the gold standard approach, may be unethical and/or infeasible. As one panelist noted, the small numbers cannot sufficiently power a study and thus necessitate new approaches, such as using patients as their own control, throughout the product development process, including in the post-approval setting.

One of the throughline considerations panelists highlighted is that multilateral communication with patient advocates integrated throughout all stages of development is necessary. Risks must be balanced with the benefits, which requires patient and clinician involvement in trial designand greater transparency and data sharing in the drug development process. This led to a discussion of the role of engagement “early and often” between and across patient groups, sponsors, and FDA staff. This was a recurring theme across several sessions.

The INTERACT meetings were specifically cited by panelists as a constructive opportunity for sponsors to have open communication with the FDA early in the development process, given that these meetings occur before the pre-IND application and are nonbinding. This early communication can also help mitigate some of the challenges that arise in the landscape of rare disease clinical trials being taken on by smaller companies. These smaller companies and rare disease drug developers in general often have only “one shot on goal”, and panelists noted there is both a patient and economic cost to not getting it right in a trial.

The session concluded with panelists discussing the potential for creating regulatory guidance based on disease archetypes. Similarities exist between some diseases, which may enable grouping them and designing trials based on disease progression, symptoms, and biological or other characteristics (e.g., rapidly fatal pediatric, slowly progressive metabolic, relapsing disorders, irreversible treatment change).

## Evaluating the Use of Internal Controls

The next session explored controls internal to the trial, including active controls, crossover designs, baseline-controlled trials, and master protocols. It began with a case study presentation on the use of intra-patient comparison in severe Hemophilia A— a rare, inherited bleeding disorder that is

carried on the X chromosome. XTEND-1 was an open-label, phase 3 study in previously treated patients who had prior recombinant or plasma-derived factor VIII treatment. This study employed an intra-patient comparison of the annualized bleeding rate between the pre-study period and the interventional period as the secondary endpoint. ALTUVIIIO (efanesoctocog alfa) was ultimately approved by the FDA in February of 2023 for routine prophylaxis on demand and for treatment and control of bleeding (including perioperative management of bleeding). Notably, it received breakthrough therapy designation and priority review from the FDA. This case study demonstrates the limitations of conducting clinical trials in rare disease populations, including small patient populations, ethical concerns around placebo or suboptimal treatment, and the heterogeneity of patients. It also provides an example where intra-patient comparisons can be useful in small rare disease populations. Further, early and frequent dialogue with regulators was identified as helpful in promoting regulatory alignment on expectations and the relevance of endpoints.

Discussion in this session emphasized patient-centric trial design. Patient perspectives highlighted the role of patients and caregivers in determining the risk-benefit of a trial, given the stakes for small and diminishing populations. Acknowledging the reality of irreversible disease progression if patients don't receive treatment for these diseases, panelists advocated exploring options other than a placebo-controlled trial first.

Another discussion point concerned the importance of data sharing in the context of rare diseases. One panelist highlighted that intra-organizational data sharing is possible where many of the clinical trials are being advanced through one foundation, as with Angelman syndrome. However, regulators, companies, and other stakeholders hold data on placebo-controlled trials and previous trials that could benefit current development efforts.

Regulators echoed the challenges raised by panelists concerning the challenges of conducting clinical trials in small populations and emphasized the need for context-specific internal controls. They explained that there are scenarios in which a randomized control arm would not be necessary, for example, if there is reliable natural history data. However, in the rare disease setting, there may be challenges in collecting robust natural history data for the disease, which is why a randomized control may be preferred. Panelists also highlighted that the type of control that is most appropriate is program-specific, considering the disease, endpoints, therapies, and available data.

The panel concluded with a discussion on the value of identifying endpoints that align with what is meaningful to the patient. One panelist raised the question of "what does success look like to a statistician versus to a mom?" Several panelists emphasized the role of the patient voice in contextualizing the data, and to this end, highlighted that a group sequential effect is an adaptive approach where the treatment is stopped if the treatment is not showing promise or if there is not enough convincing evidence to continue.

## Strategies to Optimize External Controls

The third session of the day focused on external control options, specifically natural histories, historical controls, registries, and the use of innovative statistical methods. It began with a case study presentation from the Critical Path Institute (C-Path) on the use of two natural history studies as external controls, which led to the successful approval of Givinostat for the treatment of Duchenne Muscular Dystrophy (DMD). The FDA's Division of Epidemiology accepted use of this data as confirmatory evidence of effectiveness for the product, ultimately leading to the drug's approval, with a similar response from the European Medicines Agency (EMA) not long after. C-Path emphasized the need for rigorous and timely collection of data and sharing of data with sponsors, use of natural history data when available, and early alignment on endpoints.

The next case study presented by the Cystic Fibrosis Therapeutics Development Network (TDN) discussed their efforts to develop nucleic acid-based therapies (NABTs) for the 10% of patients who do not respond to, or are not eligible for, current treatment options. The presentation highlighted the challenges of finding eligible patients due to potential bias from prior trial participation or long-term follow-ups that keep patients from trying other therapies. To address these challenges, the Cystic Fibrosis TDN, in collaboration with C-Path, is currently developing an external control repository using a fit-for-purpose prospective study to provide comparative safety and efficacy data to eventually be shared with sponsors and used in trials. Their team highlighted the use of an innovative trial design that includes individual, independent treatment trials but with a combined master protocol for the placebo groups. The team further highlighted their use of innovative statistical techniques, Bayesian and frequentist methods, and extending the randomization inference framework to avoid selection bias and unmeasured confounding variables.

Panelists shared a few ways to address some of the challenges to using external controls in small populations. For example, leveraging natural history data or past randomized control trial data to support single-arm control trials rather than relying on comparative studies. Participants also indicated that a big predictor of success is patient-centered collaboration, and that patients should be active participants in the development of external controls. For example, patient registries at the National Organization for Rare Disorders (NORD) allow patients to be the owners of their data and those registries. Furthermore, panelists emphasized that patient data should be repurposed and reused whenever possible and that broad informed consent could be appropriate for this in some cases.

Experts stated there's much to be gained by comparing approaches and lessons learned between different diseases, and that collaborative and collective approaches can help overcome some of the challenges faced in rare disease drug development. For instance, a collective registry that brings together different conditions that cause similar symptoms and medical presentations could be used in a platform trial or master protocol to make trials more feasible. Lastly, regulators suggested that standing meetings between the FDA and other regulatory bodies, such as FDA's Oncology Center of Excellence collaborations with EMA, are an opportunity to share parallel scientific advice.

## Future Directions for Controls in Small and Diminishing Populations

During the final session of the day, panelists discussed their main takeaways from the workshop and how the ideas for optimizing control strategies for clinical trials in small and diminishing patient populations can inform the Rare Disease Innovation Hub's efforts going forward.

Panelists re-emphasized many of the unique challenges associated with small and diminishing populations and noted that these challenges are only amplified when dealing with pediatric rare diseases. The variety of disease states and heterogeneity of rare diseases are additional challenges that were discussed. Panelists noted that, especially for degenerative diseases, trial participants could be in a variety of disease states. For highly heterogeneous diseases, the control arm population may not be similar enough to the therapy arm, making it difficult to confirm efficacy. Additionally, the lack of well-understood biomarkers and stratification in highly heterogeneous diseases can limit the power of statistical analysis.

Panelists emphasized the need for other ways of measuring change due to these complexities. Discussion also explored challenges of targeting data to use in natural history studies that can be used in a regulatory setting and highlighted that it is often too expensive for communities to create these databases that capture regulatory-grade data sets. Further, genetic testing may not be offered until therapies are in development or available, so prevalence isn't well recognized, limiting the ability to define endpoints and rely on a control. Panelists also expressed how many of the issues described in existing guidance documents don't apply to diminishing populations, creating a lack of clarity on how to address the uniqueness of data used in these trials and the challenges in adapting clinical data in these settings.

Discussants emphasized that a placebo-controlled study should not mean that there are patients receiving no care. Instead, these studies should be designed in such a way that the control arm receives the standard of care. By doing this, patients are guaranteed to receive the standard treatment, and by enrolling in a trial may receive additional benefits such as increased monitoring.

Panelists envisioned a way to address some of the challenges raised throughout the day, including sharing data and control arms. An opportunity exists for developers to partner with regulatory agencies and patient advocacy groups early on, so this data can be used to address obstacles like heterogeneity. Early partnership with regulatory agencies and patient groups can help identify outcomes that are meaningful to patients and clinically relevant.

There was enthusiasm from panelists around the use of real-world evidence to supplement trials where possible. For natural history data to be used as a reliable control, the natural history study needs to be designed prospectively and rigorously. The use of artificial intelligence and digital health technologies to collect this kind of data was highlighted during the discussion as a way to retain trial participants and reduce patient burden. Panelists also emphasized the need to determine a bare minimum of data needed to be considered a sufficient comparator in studies. This can support the

entire rare disease community, but particularly communities that have little funding to create registries or run natural history studies.

Regulators explained that placing more emphasis up front at the IND or design stage can help ensure studies will be informative. Additionally, a panelist suggested exploring alternate paradigms, specifically calling out the E11A Pediatric Extrapolation guidance, noting that studies should focus on addressing gaps in adult studies rather than replicating them when looking to expand therapies to pediatric populations.

Predictability and consistency were identified as necessary components in drug development for small and diminishing populations. Panelists noted that there's an opportunity to clearly define what a diminishing population is, tailor existing guidance to these populations, and find ways to disseminate learnings in this space so all rare disease communities can benefit. Further, advancing therapies could be more effective with a resource that showcases successful examples of the various archetypes and identifies gaps that, if addressed, could help resolve these challenges.

## Next Steps

The RDIH at the FDA is committed to serving as a point of collaboration and connectivity across CDER and CBER with the goal of improving outcomes for rare disease patients. A critical aspect of the work is soliciting insights and contributions from the broader rare diseases community, including patients, researchers, industry sponsors, and others.

This workshop served as the first in a series of "on the RISE" workshops on rare diseases and serves as one mechanism to accomplish the stated goals of the RDIH. The second workshop, scheduled for November 20, 2025, will focus on individualized therapies, including gene editing products and individualized antisense oligonucleotides (ASOs). Additionally, there are many additional ongoing initiatives at the FDA focused on rare diseases, including the START Pilot Program, the Rare Disease Endpoint Advancement Pilot Program, and the Collaboration on Gene Therapies (CoGenT).

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