Amy Comstock Rick, Director
Rare Disease Innovation Hub
Food and Drug Administration

Docket: FDA-2026-N-10165

Dear Ms. Rick,

The National Organization for Rare Disorders (NORD), on behalf of the one in ten Americans living with a rare disease, appreciates the opportunity to comment on the September RISE to the Challenge workshop on Statistical Considerations for Rare Disease Clinical Investigations. For more than 40 years, NORD has served as a leading patient advocacy organization for people affected by rare diseases—conditions that, under the Orphan Drug Act, affect 200,000 or fewer people in the United States—and for the organizations that represent them. Together with more than 350 patient organization members, NORD works to improve the health and well-being of people with rare diseases by advancing care, research, and public policy. Every person with a rare disease should have timely access to high quality, affordable health care and therapies that reflect their individual medical needs and informed preferences.

We are grateful for a forum to discuss important issues around statistical analysis of rare disease trials and alternative statistical approaches. However, NORD is concerned that Agency staff and outside speakers expressed a strong preference for randomized controlled clinical trials (RCTs). Preference for RCTs directly contrasts with the FDA's recently released white paper associated with the Rare Disease Framework Initiative to develop a fit-for-purpose framework for rare disease therapies. In the White Paper, FDA writes that "evidentiary tools that are routine in common disease drug development (e.g., placebo-controlled trials, primary endpoints with validated surrogate measures or meaningful clinical endpoints) may simply not be available."[1] As FDA moves forward with any draft guidance documents, further workshops, internal training, or other efforts to follow-up on this RISE Workshop, NORD encourages FDA to keep in mind the spirit of the Rare Disease Framework Initiative.

[1] A New Framework for Rare Disease Review available at https://www.fda.gov/media/195694/download?attachment

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FDA has often acknowledged the challenges of rare disease trials, including the small population size, disease heterogeneity, lack of accepted endpoints, and lack of natural history data. Another challenge not discussed during this workshop is the lack of clinical practice guidelines or standards of care for rare diseases. Some panelists assumed that patients would enroll in a placebo-controlled trial to obtain expert care. However, this is rarely the case - often the experts providing clinical care to patients with rare diseases, particularly pediatric patients, are the same experts serving as investigators in rare disease clinical trials. In addition, patients on control arms of trials receive the standard of care; when there is no standard of care, patients may have to stop taking experimental or that are helping in order to participate. The discussion at this workshop did not discuss the ethical need for rescue protocols, which lower the utility of the trials from a statistical perspective.

Many FDA speakers stated a clear preference for RCTs to reduce uncertainty.[2] And external experts invited to speak included those with a perspective that anything other than an RCT is "less than".[3] There are situations where RCTs are useful; however, they should not be the default.[4] This is particularly the case for rare disease clinical trials.

[2] Rebecca Chiu, PhD, Office of Biostatistics, CDER, "When we don't fully understand how a disease is going to progress or how an intervention works, randomization really provides a basis for confidently attributing any observed improvements to the treatment itself rather than other factors. Now, certainly, as I said, there are circumstances where a non-randomized trial can provide that reliable inference, they are less frequent and they require some pretty careful scrutiny." RISE to the Challenge: Statistical Considerations for Rare Disease Clinical Investigations, 2026.

[3] Thomas Fleming, Professor Emeritus, Biostatistics Professor of Biostatistics and Statistics, University of Washington. "Often properly addressing these principles is very challenging but still achievable. And the first of these five principles is that pursue randomized clinical trials whenever possible, even in rare disease settings, to greatly enhance reliability by preventing the risks of significant bias due to systematic confounding of the true treatment effects with the effects of strongly prognostic baseline factors. However, non-randomized trials can provide reliable evidence, especially when the intervention provides truly compelling effects relative to standard of care and especially if the mechanism of action is highly understood, gene replacement therapy, or if there'd be no spontaneous improvement in standard of care, such as when using the endpoint objective response rate in oncology settings." RISE to the Challenge: Statistical Considerations for Rare Disease Clinical Investigations, 2026.

[4] See also: Citizen Petition from Haystack et al, filed April 7, 2026, Docket FDA-2026-P-3666.

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NORD was pleased to hear the speakers discuss the utility of novel trial designs. From using historical controls,[5] to external controls,[6] to novel statistical methods,[7] Agency staff and panelists expressed willingness to engage in trial designs that are not the standard RCT.[8][9][10]The workshop would have benefited from further discussion of how to use statistical tools to analyze data generated outside of RCTs that are not perfect themselves (e.g., where there is not a "well understood natural history") since rare disease development programs rarely follow a pre-specified path.

NORD agrees that rare disease patients do not deserve lower efficacy, however, it has been made clear that rare disease patients may accept greater uncertainty and often

[5] Rebecca Chiu, PhD, Office of Biostatistics, CDER, "So we may look to other sources of information that might be natural history studies, historical controls, related populations to supplement our trial data. And we might think about things like Baysian approaches with informative priors that offer a principled way to try and incorporate that external information into the analysis. We may also be able to rely on longitudinal and repeated measures to try and extract as much information as we can from just a single patient.
The second category is using or leveraging the information already available but more efficiently. So even with a fixed sample size, there's often room to improve through a smarter design or a different analysis choice. Um so just a couple examples here. We have covariant adjustment for known prognostic factors. This is a well-known approach and it's pretty straightforward but often underutilized for efficiency gains. We can also think about adaptive and group sequential designs that allow us to build in checkpoints where we evaluate accumulating evidence and adjust the trial accordingly." RISE to the Challenge: Statistical Considerations for Rare Disease Clinical Investigations, 2026.

[6] Mark Levenson, Director, Office of Biostatistics, CDER "FDA regulations and laws permit other controls…we can approve drugs on external controls and we do." RISE to the Challenge: Statistical Considerations for Rare Disease Clinical Investigations, 2026.

[7] John Scott, CBER "We haven't we haven't really gotten into the nitty-gritty, but we're sort of circling around the idea of adapting decision criteria to the context. FDA recently published a draft Baysian guidance where we also raised that concept." RISE to the Challenge: Statistical Considerations for Rare Disease Clinical Investigations, 2026.

[8] Ying Yuan, UT MD Anderson, "In general, for rare disease, I think we should look at alternative Paradigm…because the sample size is limited and… Baysian provides a very promising alternative approach especially when we know we won't have enough power. So given what we want, it's what kind of evidence we collect from the data. What's the probability the treatment is better than control? What's the probability patient achieves clinical meaningful improvement?" RISE to the Challenge: Statistical Considerations for Rare Disease Clinical Investigations, 2026.

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have a higher tolerance for risk than people with more common, well-treated diseases.[11] NORD appreciates the distinction between uncertainty and bias and agrees with the speakers that uncertainty is tolerable but bias negates the utility of the trial. The need to ensure an appropriate benefit-risk balance can only come from working with patients and caregivers.

NORD agrees with many of the speakers regarding the need to measure meaningful endpoints. Again, these are best understood through the context of the patient and caregiver. The goal of a trial is not to generate statistically significant results, it is to generate evidence that informs meaningful treatment decisions. This can only be done when considering outcomes that matter to patients and if patients are willing to participate. The most well-designed trial is useless if it is not feasible, or if it remains unenrolled.

Recommendations

NORD recommends that FDA begin by identifying the evidence necessary to establish treatment effectiveness, rather than treating the feasibility of an RCT as the threshold question. Nonrandomized designs should be evaluated on their scientific merits and fitness for purpose, not presumed inferior solely because they lack randomization. Scientific rigor must be met but must also be tailored to the disease and potential intervention.

We further recommend that FDA continue expanding education for internal and external stakeholders on rigorous, fit-for-purpose trial design. Such efforts should incorporate multidisciplinary expertise in study design, endpoint development, research ethics, and methods for generating reliable evidence in rare diseases.

NORD looks forward to continued collaboration with FDA and other stakeholders to develop clinical trials that minimize burdens on patients and caregivers while maximizing scientific rigor, meaningful participation, and potential benefit.

Sincerely,

Cara Tenenbaum

Cara Tenenbaum
Director of Regulatory Affairs
National Organization for Rare Disorders

[11] Morel T, Aymé S, Cassiman D, Simoens S, Morgan M, Vandebroek M. Quantifying benefit-risk preferences for new medicines in rare disease patients and caregivers. Orphanet J Rare Dis. 2016 May 26;11(1):70. doi: 10.1186/s13023-016-0444-9. PMID: 27225337; PMCID: PMC4881055 available at https://pubmed.ncbi.nlm.nih.gov/27225337/

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