DEPARTME

Food and Drug Administration

[Docket No. FDA-2026-N-10165]

Statistical Considerations for the Design of Rare Disease Clinical Investigations; Establishment of a Public Docket; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for information and comments

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is establishing a public docket to collect feedback on statistical considerations for rare disease clinical investigations. This docket is open in conjunction with a Rare disease Innovation, Science, and Exploration (RISE) Workshop on the same topic. Feedback is welcome both on the attached pre-read documents and on the content covered in the Workshop itself.

DATES: Either electronic or written comments on the notice must be submitted by November 13, 2026.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 13, 2026. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be

posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2026-N-10165 for "Statistical Considerations for the Design of Rare Disease Clinical Investigations; Establishment of a Public Docket; Request for Information and Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information

you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Philipa Friedman, Rare Disease Innovation Hub, rdinnovationhub@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The RISE Workshop series, co-convened by the FDA Rare Disease Innovation Hub and the Duke Margolis Institute for Health Policy, brings together innovators in drug development, rare disease research, patient advocacy, and regulatory science to discuss challenges in the development of medical products for rare diseases that are common to multiple rare diseases or a

class of diseases and for which evolving science offers innovative solutions. The workshops focus on cross-cutting or common issues and do not cover specific products under review by the Agency.

The September 29, 2026, RISE Workshop focuses on statistical considerations for rare disease clinical investigations. Statistical considerations affect numerous aspects of drug development, testing, and review, including clinical trial design and measurement of product effectiveness. Statistical review for rare disease products can be particularly complex, and it requires significant attention to the nuance of the disease state and specific product. Small patient populations constrain sample sizes, limit statistical power, and increase the risk of inconclusive results, yet the urgency of patient need makes timely, reliable evidence critically important. Every clinical investigation design decision involves trade-offs between efficiency and reliability, as well as feasibility and rigor. Meeting this challenge requires both scientific innovation and a shared commitment to transparency about those trade-offs.

II. Issues for Consideration and Request for Information

FDA is seeking feedback from the public – including rare disease medical product developers, disease advocates, and researchers – on the appropriate use of tailored approaches to statistical review of rare disease medical products. FDA has developed two pre-read documents that inform the September 29, 2026, RISE Workshop; one document discusses statistical considerations for clinical trials of rare disease drugs and biologics, and the other document covers statistical considerations for clinical studies of rare disease medical devices. FDA welcomes feedback on either or both of the pre-read documents, as well as feedback related to the content discussed in the RISE Workshop itself.

The pre-read documents are attached in their entirety, and FDA is specifically seeking information that addresses the following discussion questions from the pre-read documents:

For drugs and biologics

1. To what extent should we consider adjusting standard success criteria (e.g., significance thresholds) in a rare disease trial and how should disease severity, feasibility constraints, and the availability of corroborating evidence factor into that decision?
2. What would make randomized designs more acceptable and feasible to patients and sponsors in rare disease settings and what role can enhanced medical care for participants in the control arm, patient engagement, and innovative design features play in addressing the concerns of patients and advocacy communities? Examples may include:
    a. Ensuring that participants on the control arm always receive treatment and care that meets or exceeds the standard of care they would receive in clinical practice if they did not participate in the study.
    b. Incorporating sequential analyses to ensure that the study stops as soon as possible if there is convincing evidence of efficacy or continues if results are promising but not yet sufficient to inform reliable conclusions.
3. Endpoint selection in rare diseases involves balancing what matters most to patients, what is statistically feasible, and what regulators can accept as evidence of benefit. Where does the rare disease and statistical community see the greatest unmet need in this space — and what would most help move the field toward endpoints that are both meaningful to patients and credible to regulators?
4. Which efficiency-enhancing strategies offer the most feasible and meaningful gains in rare disease studies — and what practical barriers currently stand in the way of their wider adoption?

For medical devices

1. For new Class III devices for small patient populations, what are important considerations for the premarket-postmarket data shift specific to products serving small populations? What mechanisms (e.g., registries, electronic health records, post-approval studies) would best support timely, reliable postmarket data collection? *(Note: the pre-*

read document uses brain-computer interface (BCI) devices for amyotrophic lateral sclerosis (ALS) as a case example.)

2. Under what clinical situations and statistical conditions can a single-arm device study with a performance goal or external control provide acceptable evidence of reasonable assurance of safety and effectiveness for devices for small patient populations — and what pre-specifications are needed to ensure such designs provide reliable and acceptable evidence? *(Note: the pre-read document uses BCI devices for ALS as a case example.)*
3. What design features would make an external data source appropriate for future pivotal studies in small populations? What infrastructure should be built proactively and by whom? *(Note: the pre-read document uses BCI devices for ALS as a case example.)*
4. What sources of prior information — feasibility studies, natural history data, international experience, prior device generations — are most appropriate and credible in small patient populations, and can hierarchical borrowing and Bayesian adaptive designs meaningfully improve efficiency and accelerate reliable evidence generation in this space?

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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