ACRO Innovate Advocate Collaborate

November 21, 2025

Janet Goldberg
Center for Biologics Evaluation and Research
Grace R. Graham,
Deputy Commissioner for Policy, Legislation, and International Affairs
Food and Drug Administration

RE: ACRO comment submission on *Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations* Docket (FDA-2025-D-3403)

Dear Ms. Goldberg and Ms. Graham,

Founded in 2001, the Association of Clinical Research Organizations (ACRO) is a non-profit trade association representing the world's leading clinical research and technology organizations, which provide specialized services that are integral to the development of drugs, biologics and medical devices that enable patients to live longer, healthier, and more productive lives. ACRO members provide a wide range of services and digital technologies across the entire spectrum of development – from pre-clinical, proof of concept, and first in human studies through post-approval, pharmacovigilance, and health data research. ACRO member companies employ nearly 400,000 people worldwide and conduct research in every global region.

General Comments

ACRO welcomes the Draft Guidance for Industry on *Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations*. As with all guidance documents, this draft guidance helps enable effective drug development. Biomedical innovation abhors a vacuum. Regulatory uncertainty and unpredictability can create industry caution and risk aversion about the adoption of innovative approaches to clinical research. Guidance documents – including this draft guidance on innovative design for CGTs – help de-risk the expensive, lengthy drug development process by providing transparency into the FDA's current, best thinking through pragmatic, risk-based recommendations. Because of their legally non-binding status – providing recommendations that enable flexibility – guidance documents foster a nimble, agile approach to drug development and provide a stable, predictable business environment where drug developers can make business decisions with confidence. A key component of FDA's leadership amongst regulators worldwide is thanks to its prescient issuance of guidance documents on emerging, timely issues.[1]

[1] Just a handful of examples of FDA's global leadership in regulatory innovation are the following guidances:

- *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products* (draft) https://www.fda.gov/media/184830/download
- *Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice* (draft) https://www.fda.gov/media/181871/download
- *Conducting Clinical Trials with Decentralized Elements* (final) https://www.fda.gov/media/167696/download
- *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (final) https://www.fda.gov/media/155022/download

The integration of these draft guidance recommendations on the planning, design, conduct, and analysis of cell and gene therapy trials with the principles described in other existing FDA guidance demonstrates the FDA's commitment to increased efficiency for the development and review of cell and gene therapy products. In particular, ACRO welcomes the explicit recognition by the Agency of the challenges relating to developing drugs and biological therapies for rare diseases and the importance of innovative trial designs that are both feasible and rigorous. This draft guidance provides recommendations and guidance on cell and gene therapies for small populations and promotes a range of trial designs that can facilitate the generation of the robust evidence needed for product approval while also addressing the challenges inherent to studies with small sample sizes and potential heterogeneous disease manifestation. ACRO also notes and welcomes the need for early engagement with the Agency when planning such studies.

Specific Comments

Lines 53-60
ACRO welcomes the draft guidance's explicit reference to statutorily authorized evidence generation standards. We applaud the intentional linkage of the use of innovative trial designs with the generation of data that can demonstrate substantial evidence of effectiveness as defined in Section 505(d) of the Federal Food, Drug, and Cosmetic Act.[2] The FDA is recognized by global regulators as a forward-leaning Agency that maintains the gold standard for scientific validation as the bulwark for safety and efficacy; data integrity; and evidence generation. This draft guidance fortifies FDA's leadership in regulatory science:

> *Given the urgent need for safe and effective products to treat serious and severely debilitating diseases in small populations, FDA recognizes the importance of innovative and efficient trial designs, including selection of appropriate endpoints that are feasible and capable of generating the necessary evidence for approval. Trial designs that are novel but maintain a high degree of rigor in data collection and interpretability are essential to meet these urgent needs. The recommendations herein are intended for sponsors developing CGTs intended for use in small populations to leverage the use of innovative trial designs to simultaneously expedite drug development and* ***generate data necessary to demonstrate substantial evidence of effectiveness*** [Lines 53-60, emphasis added].

Lines 77-103
ACRO welcomes the details on single-arm trials utilizing participants as their own control. The example regarding potential use in universally degenerative conditions is helpful, as is the explanation of the possible issues arising when using this method in trials with conditions that fluctuate.

[2] Section 505(d) of the Federal Food, Drug, and Cosmetic Act: *"The term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.*

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Lines 107-118
ACRO requests FDA to consider the inclusion of illustrative case examples to clarify and illuminate the draft guidance recommendations.

Line 120-138
Externally Controlled Studies require a detailed plan for harmonizing endpoint definitions, visit windows, and covariates between the current trial and external data. ACRO notes that this section of the draft guidance provides an overview but does not provide details, instead directing readers to the draft guidance on *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). Due to the need for robust planning when using this option, ACRO recommends the expeditious finalization of this February 2023 draft guidance on Externally Controlled Trials.

Lines 143-168
ACRO notes the ongoing consultation on ICH E20 *Adaptive Designs for Clinical Trials* and the minor differences in terminology between the ICH E20 draft and this draft guidance (e.g., "sample size reassessment designs" vs "sample size adaptation"). Where possible, ACRO requests the Agency to consider harmonization in terminology, or an explanation of the differences in terminology in the final version. ACRO also recommends inclusion of a cross-reference to ICH E20 in the FDA guidance.

Lines 219-220
ACRO notes that "Sponsors may consider trial designs that incorporate surrogate endpoints, biomarkers, or intermediate clinical endpoints prior to symptom onset if applicable."
We welcome further clarification on the path for validation or qualification of any surrogate or biomarker used as a primary efficacy endpoint, such as the minimum level of evidence for surrogates when leveraging biological, analytical validity, epidemiological, and clinical correlation.

Lines 221-223
ACRO welcome the recognition that "In some cases, endpoints measured with digital health technologies (DHTs) may be better able to capture meaningful changes in clinical function."
ACRO welcomes this important reference to DHTs and asks the Agency to consider further elaboration of this point in the final guidance in order to enable and facilitate greater adoption of DHTs.

Thank you for the opportunity to provide input on this draft guidance. Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions.

Respectfully submitted,

Karen Noonan

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