Innovative Designs for Cliincal Trials of Cellular and Ge py Products in Small Populations

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Draft Guidance For Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations
Draft Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to sponsors who are planning clinical trials of cell and gene therapy (CGT) products intended for use in a disease or condition that affects a small population—generally one that meets the definition of a rare disease or condition under section 526(a)(2) of the FD&C Act (21 U.S.C. 360bb(a)(2)). It describes FDA requirements and provides considerations for the use of various clinical trial designs and endpoints to generate clinical evidence to support product licensure. This guidance expands on principles described in FDA's existing guidance documents related to this topic,[2, 3] by providing additional recommendations for the planning, design, conduct, and analysis of cell and gene therapy trials to facilitate FDA's assessment of product effectiveness.[4]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This draft guidance has been prepared by the Center of Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] See guidance for industry: *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023), available at https://www.fda.gov/media/119757/download.

[3] See draft guidance for industry: *Rare Diseases: Natural History Studies for Drug Development* (March 2019), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] For a biological product, like CGT, to be licensed under section 351 of the Public Health Service Act, a sponsor must demonstrate, among other things, that its product is safe, pure, and potent. Potency has long been interpreted to include effectiveness. See 42 U.S.C. 242; see also 21 CFR 600.3(s). FDA has also generally considered "substantial evidence" of effectiveness to be necessary to support licensure. See section 505(d) of the FD&C Act (21 U.S.C. 355(d)) and 21 CFR 314.126 (discussing characteristics of adequate and well-controlled studies used to establish effectiveness).

II. BACKGROUND

On September 30, 2022, the FDA User Fee Reauthorization Act of 2022 was signed into law. The Act includes the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA), *PDUFA VII: Fiscal Years 2023 – 2027 FDA*,[5] which provides FDA with resources to help maintain a predictable and efficient review process for human drug and biological products.

This guidance was created as part of FDA's response to the PDUFA VII commitment to increase efficiency in the development of CGT products.[6] FDA recognizes the significant challenges in developing drug and biological products for rare diseases, including small population sizes where limited data exist to support regulatory decision-making, sparse natural history knowledge, incompletely understood molecular pathogenetic mechanisms, and molecular and phenotypic heterogeneity. These development challenges are further compounded by unique considerations for product manufacturing and the generation of nonclinical evidence to support a product's pharmacology and toxicology profile for CGT products. On the other hand, CGT products for rare diseases can be uniquely positioned to allow the tailoring of individual programs, due to the targeted nature of the products, which often directly correct or modify a gene known to cause phenotypic disease. Consideration of innovative clinical trial design features early in product development can help optimize the quality of data generated while maximizing the use of each data point collected throughout the development process.

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.

In certain cases for common diseases with significant methodological challenges pertaining to conducting trials, the innovative trial designs and participant selection considerations discussed below may be appropriate. We recommend that, in such situations, the sponsor contact the relevant review division to discuss further.

III. INNOVATIVE CLINICAL TRIAL DESIGNS

Sponsors may consider a variety of innovative clinical trial approaches for developing CGTs in small populations. The recommendations below address a non-exhaustive list of trial design(s) that sponsors may consider when planning clinical trials to develop CGT products intended for

[5] See www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027.

[6] Section I.0.2.b. of the PDUFA VII commitment letter states that, "[B]y the end of FY 2025, FDA will issue a draft guidance on the evaluation of efficacy in small patient populations using novel trial designs and statistical methods, and how these concepts can be applied to more common diseases."

use in small populations.[7] FDA recommends that sponsors discuss options for innovative clinical trial designs with the Agency as early as possible.[8, 9, 10]

A. Single Arm Trials Utilizing Participants as Their Own Control.

This design leverages an internal, baseline control strategy where a participant's response to therapy on a given measure is compared to their baseline status on that measure. In this way, the measure could be used to inform one or more endpoint(s) to determine the outcome of the trial. This scenario is predicated on having reliable and complete data to establish the participant's baseline on the relevant endpoint. Establishing participants' baselines can be achieved by prospectively collecting relevant data in a lead-in period in the trial over a certain duration before administration of the investigational product. Alternatively, baseline data can be collected retrospectively if data on the relevant endpoint are available and reliable.

When considering such a study design, sponsors should account for the overall course of the illness and goal of treatment. Self-controlled studies can be particularly persuasive when a condition is universally degenerative in all affected individuals, and the intervention is expected to lead to improvement. However, in conditions that have waxing and waning course, or when the CGT is intended to slow rather than reverse progression, it can be challenging to demonstrate effectiveness without a concurrent control. For such conditions, it is important to ensure that enrollment criteria do not lead to subjects beginning the trial with unusually severe symptoms. If a large number of subjects are at a "peak" of their symptom severity at the time of treatment initiation, any subsequent improvement in symptoms could be due to either the treatment itself or to a natural tendency for symptoms to return to a more stable level after peaking (sometimes called regression to the mean). This can create significant challenges to interpretation of trial results, particularly in cases where the observed treatment effect size is not very large. Finally, the selection of objectively measured endpoints that are not effort-dependent is critical to interpreting results from self-controlled or other non-blinded trials. We also direct investigators to relevant ICH scientific guidelines[11] for additional methodological considerations.

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[7] One such approach may be to consider a decentralized trial design. See guidance for industry: *Conducting Clinical Trials With Decentralized Elements* (September 2024), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/conducting-clinical-trials-decentralized-elements.

[8] Interactions with Office of Therapeutic Products | FDA.

[9] See draft guidance for industry: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,* available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products| . When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[10] See the guidance for industry: *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products* (December 2020), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interacting-fda-complex-innovative-trial-designs-drugs-and-biological-products.

[11] See International Council for Harmonisation document E10: *Choice of Control Group in Clinical Trials* (July 2000).

B. Disease Progression Modeling

Disease progression modeling is a quantitative approach that characterizes the natural history of a disease over time, incorporating factors such as biomarker trajectories, clinical endpoints, and patient heterogeneity to inform clinical trial design and regulatory decision-making. Key considerations include selecting appropriate mathematical frameworks, defining meaningful clinical endpoints that correlate with disease progression, and accounting for covariates such as baseline disease severity, demographics, and concomitant treatments that may influence progression rates. Major challenges include the inherent variability in disease progression across patients, the often lengthy observation periods required to capture meaningful changes, potential confounding from standard-of-care evolution, and the statistical complexity of validating models across diverse populations, particularly if extrapolating to subgroups not well-represented in the modeling dataset.[12]

C. Externally Controlled Studies

Externally controlled clinical trial studies utilize historical or real-world data from patients who did not receive the investigational treatment as the comparator group, rather than or in addition to enrolling a concurrent control arm within the same study protocol. External control and trial populations should be as similar as possible regarding known factors that can affect the outcome variable, including baseline characteristics, disease severity, standard of care, and prognostic factors, while also accounting for differences in data collection methods, outcome definitions, and follow-up procedures between datasets.

Importantly, before choosing to conduct a clinical trial using an external control arm as a comparator, sponsors and investigators should consider the likelihood that such a trial design would be able to distinguish the effect of a drug from other factors that impact the outcome of interest. The suitability of an externally controlled trial design warrants a case-by-case assessment, informed by issues including heterogeneity of the disease (e.g., clinical presentation, severity, prognosis), preliminary evidence regarding the drug product under investigation, the approach to ascertaining the outcome of interest, and whether the goal of the trial is to show superiority or non-inferiority. For additional information, see FDA guidance on using external controls.[13]

[12] One population that is frequently underrepresented in trials are pediatric participants. We encourage investigators to consider December 2000 guidance *E11: Clinical Investigation of Medicinal Products in the Pediatric Population* when modeling disease progression. The guidance is available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population.

[13] See the draft guidance for industry: *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

D. Adaptive Clinical Trial Designs

Adaptive clinical trial[14] designs allow for prospectively planned modifications to one or more aspects of the design based on accumulating data from participants in the trial. Clinical trials that are intended to demonstrate the safety and effectiveness of a CGT can contain a variety of adaptive features that may be appropriate in different circumstances to generate robust data and expedite drug development. These include:

i. group sequential designs - allow for early trial termination due to convincing evidence of effectiveness or futility;
ii. sample size reassessment designs - allow for adjustments to study size based on accumulating data;[15]
iii. adaptive enrichment designs[16] - modify enrollment after prespecified interim analysis to focus on subpopulations most likely to benefit from an intervention;
iv. adaptive dose-selection designs - can select a dose and confirm the effectiveness of that dose within the same study.

All these adaptive features use accumulating trial data to modify the trial design according to a prospectively defined plan. As such, adaptive designs can improve the chance of trial success in situations with limited pre-trial clinical data by allowing learning from empirical evidence. To preserve trial integrity, rigorous planning, careful implementation, and comprehensive documentation of approaches can support the ability of the trial to reliably achieve the stated objective in a timely manner.[17] Many adaptive techniques are potentially applicable to both single arm and controlled trials. With all adaptive designs, great care should be taken to adequately prespecify the adaptative procedure to avoid a potentially inflated chance of erroneous conclusions; this is particularly critical in the case of adaptations in single arm or other open label trials.

E. Bayesian Trial Designs

Bayesian designs can explicitly incorporate clinical data external to the trial in analyses, effectively leveraging available relevant information. This can include use of existing control data to augment a concurrent control group, thereby reducing the sample size

[14] See the guidance for industry: *Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry* (November 2019), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.

[15] Accumulating data may be used, for example, to conduct interim analyses that allow for expedited approvals or to support crossover design studies. In some cases, designs that allow patients initially assigned to control to receive the investigational therapy after primary endpoint ascertainment may help motivate subject enrollment. These designs ensure that all participants can potentially receive a promising investigational therapy, addressing concerns about being assigned to a potentially less effective control.

[16] See the guidance for industry: *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products.

[17] Fleming, TR, et al., 2008, Maintaining Confidentiality of Interim Data to Enhance Trial Integrity and Credibility, Clin Trials 5(2):157-167.

needed for the concurrent controls. In rare cases, there may be relevant comparative prior information available that can be leveraged to reduce the overall sample size of a controlled trial. Bayesian approaches can also be used to facilitate complex adaptive designs, to aid in establishing effectiveness in pediatric populations after effectiveness has been demonstrated in adults, and to improve estimates of treatment effects in subgroups. Bayesian designs can also potentially incorporate alternative trial success criteria based on benefit-risk considerations or decision theoretic approaches that evaluate the likelihood and magnitude of clinical benefit in the overall context of product risk and/or medical need.

F. Master Protocol Designs

Master protocols[18] are protocols designed with multiple substudies. Examples of trial types that use a master protocol include platform or umbrella designs in which multiple interventions can be studied concurrently with a common control group, and basket designs in which a single CGT product can be evaluated in multiple conditions or disease subtypes. Such designs could incorporate cohorts with different manifestations of a disease to potentially address challenges in measuring the treatment effect in a disease setting with very heterogenous clinical presentations.

IV. CONSIDERATIONS FOR PARTICIPANT SELECTION

A. Treatment Landscape Considerations

CGT development programs are often intended for use in a rare disease or condition that presents a significant unmet medical need. Often, any available therapy manages symptoms or addresses the underlying pathophysiology of the disease with limited efficacy. As such, trial entry criteria that require participants to have exhausted available therapies may not be appropriate or may be unnecessarily exclusive. Sponsors are encouraged to carefully consider the treatment landscape and the effectiveness of available therapies prior to determining whether restriction of the trial to those who are no longer responding to available treatments is appropriate, and whether such an approach would facilitate generalizability of study results should the product be approved.

[18] See the draft guidance for industry: *Master Protocols for Drug and Biological Product Development* (December 2023), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-drug-and-biological-product-development. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

B. Symptom Status Considerations

In the early phase of some genetic diseases, symptoms may be mild or absent. In some cases, there may be uncertainty regarding whether all affected patients will develop symptoms, at what timepoint, and how those may progress or change over time. Sponsors should carefully account for this at the study design phase, specifically with respect to efficacy endpoint selection and the study analysis plan. Sponsors may consider trial designs that incorporate surrogate endpoints, biomarkers, or intermediate clinical endpoints prior to symptom onset if applicable. Sponsors are strongly encouraged to interact with FDA early to discuss efficacy endpoints. In some cases, endpoints measured with digital health technologies[19] (DHTs) may be better able to capture meaningful changes in clinical function.

C. Study Population Representativeness

In most cases, it is appropriate in early trials of CGT for sponsors to permit enrollment of broadly representative populations affected by the disease. This can help increase the pool of participants available to evaluate safety and identify product dosages that may be appropriate to investigate in future studies. Broad representativeness in the enrolled population may also permit the collection of data that may be relied upon to extrapolate to populations beyond those enrolled in pivotal study(ies). When appropriate, generally based on the product's mechanism of action, broad representation of those with common genetic variants and phenotypes should be allowed to enroll.

Sponsors who are developing CGT products to treat pediatric diseases or conditions should consider whether and how they will incorporate additional safeguards for pediatric subjects in clinical investigations.[20] FDA regulations at 21 CFR part 50, subpart D[21] address requirements for permission by parents/guardians and, where appropriate, assent by children, the level of risk posed to children as subjects, and additional safeguards. In accordance with 21 CFR 50.50, an Institutional Review Board (IRB) reviewing a clinical investigation involving children as subjects must approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51, 50.52, or 50.53 and the requirements of all other applicable provisions of Subpart D. The IRB must assess the level of risk that the interventions and procedures included in a clinical trial would present to pediatric subjects to determine whether they involve no greater than minimal risk (21 CFR 50.51), greater than minimal risk but present the prospect of direct benefit

[19] Medical Devices that Incorporate Sensor-based Digital Health Technology

[20] A detailed discussion of the FDA requirements for safeguarding pediatric subjects in clinical investigations (21 CFR part 50 Subpart D) (Subpart D)) is beyond the scope of this guidance, which briefly highlights only certain considerations. In addition to the Subpart D regulations, the FDA has published other documents that address the inclusion of children as subjects in clinical investigations, including the preamble to the Subpart D final rule cited in footnote 21, the guidances cited in footnotes 12 and 22, and the draft guidance *Research Involving Children as Subjects and Not Otherwise Approvable by an IRB: Process for Referrals to FDA and OHRP* (March 2023), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/research-involving-children-subjects-and-not-otherwise-approvable-institutional-review-board-process.

[21] See also Final Rule: Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products. 78 FR 12937 (February 26, 2013).

to individual subjects (21 CFR 50.52), or no more than a minor increase over minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the subjects' disorder or condition (21 CFR 50.53); depending on the level of risk found by the IRB, additional requirements may apply. If the IRB concludes that a clinical investigation does not meet the requirements of these provisions, a further process under 21 CFR 50.54 may be applicable if additional criteria are met. Trials of CGT products may present more than a minor increase over minimal risk, and in such cases would need to meet the requirements of 21 CFR 50.52 or 50.54.

To support determinations on including pediatric participants in a clinical investigation, sponsors should take an approach that would expedite safe development of CGT to treat diseases or conditions in children. When planning a CGT clinical development program, sponsors should consider whether the disease affects the pediatric population differently than adults with the same disease; whether the data generated in adults would be relevant to the pediatric population with the condition; and what available data and information from their clinical development program and from other sources can support an assessment of the prospect of clinical benefit in pediatric patients. Such data could be derived from nonclinical (e.g., animal studies, in vitro studies, in silico), and clinical evaluation (e.g., clinical pharmacology studies, clinical trials). Pediatric enrollment into studies for CGTs without prior investigation in adults may be considered, provided scientific necessity has been assessed, and an appropriate clinical trial design with adequate safety monitoring can be developed and approved by the IRB and reviewed by the FDA, as appropriate.[22, 23]

[22] See draft guidance for Industry, Sponsors, and IRBs: *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[23] "IRBs should consider the scientific necessity of conducting a clinical investigation in children. It may be more efficient to consider scientific necessity prior to assessing risk and benefit under 21 CFR part 50, subpart D. Children should not be enrolled into a clinical investigation unless their participation is necessary to answer an important scientific and/or public health question directly relevant to the health and welfare of children. For example, for products that are being developed for use in adults and children, if effectiveness in adults can be extrapolated to children, then effectiveness studies in adults should be conducted to minimize the need to collect effectiveness data in children." Id.