November 24, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**RE: Docket No. FDA-2025-D-3403: Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations; Draft Guidance for Industry**

Dear Sir or Madam,

On behalf of the Pediatric Inclusion Alliance, we are pleased to submit comments on FDA's "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations," Draft Guidance for Industry. We appreciate FDA's attention to the planning of clinical trials for cell and gene therapy (CGT) products for use in small populations. Of specific importance for the Pediatric Inclusion Alliance is the development of clinical trial designs that include children for early onset diseases and conditions.

## About the Pediatric Inclusion Alliance

The Pediatric Inclusion Alliance (Alliance) is devoted to full, active collaboration among all stakeholders committed to achieving earlier inclusion of children in clinical trials across all diseases and conditions without compromising safety. For far too long, children have had to wait years for access to safe, effective therapies, often already approved for adult populations. These therapies might well have been even more effective for younger patients if administered at the best time for them.

By combining a deep understanding of the needs of pediatric patients and their families, technical expertise, and real-world experience in medical research and therapy development, knowledge of regulatory guidance and processes, public policy, regulatory knowledge, and public policy understanding, the Alliance is a united collaborative of stakeholder groups committed to ensuring that children have the earliest opportunity to access safe and effective therapies when those therapies are most likely to have maximum benefit to them. This is especially true for early onset genetic disorders, the affected populations for which could benefit from earlier inclusion of children in CGT clinical trials.

## General Considerations for Early Pediatric Inclusion

Most rare diseases begin in childhood or exclusively affect children.[1] In many rare pediatric diseases, time is of the essence and delays in treatment result in irreversible disease progression. Yet, pediatric patients are often excluded from early clinical trials. As a consequence, many children with rare diseases either suffer from needless delays in treatments or receive medications off-label, potentially exposing them to unstudied risks.[2]

Children who have rare diseases with early onset, rapid progression, and in some cases mortality, cannot wait for clinical trials in adults to be done before it is their turn. Additionally, for diseases where emerging therapeutics are personalized and exceedingly expensive to produce, such as cellular or gene therapies, traditional routes for patient access are functionally closed for those who do not meet inclusion criteria at the onset. Compassionate Use Access requires that the therapy be provided outside of the trial, which in the case of personalized cellular therapies is cost prohibitive outside of clinical trial.

Completing clinical trials in adults first and delaying pediatric inclusion "to ensure pediatric safety" is a flawed approach if it means that children with rare diseases are denied access to interventions during a narrow timeframe when it might alter the disease state and instead suffer severe morbidity or mortality. While likely beyond the scope of this guidance, the same holds true for children with more common diseases that may still cause morbidity or even mortality. Furthermore, participation in clinical trials allows children and their families, including those affected by disabling or life-threatening diseases, to contribute to the advancement of pediatric medicine for future generations, reflecting a goal shared by many in such disease communities to make a lasting impact. With advanced knowledge, understanding, and technology, thinking has evolved, and it is scientifically and ethically imperative for early pediatric inclusion in clinical trials.

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[1] C. E. Lee, et al., (2020, May 22) "Rare Genetic Diseases: Nature's Experiments on Human Development," iScience, vol. 23. https://www.sciencedirect.com/science/article/pii/S2589004220303084

[2] Shah, S. S. et al. Off-label drug use in hospitalized children. Arch. Pediatr. Adolesc. Med. 161, 282–290 (2007).

Regulators and institutional review boards are increasingly recognizing that for serious pediatric conditions with unmet need, carefully conducted early-phase trials in children are ethically permissible and indeed necessary.[3] "The principle of justice in research ethics dictates that children, who cannot consent for themselves, should not be unfairly excluded from the benefits of research. Historically, overprotection led to the concept of "therapeutic orphans", where children were deprived of advances in medicine available to adults.[4]

The Alliance thanks FDA for mentioning consideration of pediatric clinical trials, but we urge FDA to emphasize inclusion of children with rare disease at the initial stage of consideration and design of clinical trials rather than after adult clinical trials are well underway.

Furthermore, we applaud the urgency and flexibility expressed on the need for safe and effective products to treat serious diseases in small populations and FDA's willingness to be flexible and consider innovative and efficient trial designs, including appropriate endpoints as evidence for approval. As discussed below, both urgency and flexibility are very relevant in the context of pediatric rare diseases.

We also agree with FDA's sentiment on page 2 that "consideration of innovative clinical trial design features early in product development can help optimize the quality of data generated…" This is particularly true with pediatrics. Scientifically, there are often developmental differences in drug absorption, metabolism, excretion, and immune responses that make it difficult to extrapolate safety data from adults to children. [5] For example, immature hepatic and immune functions in young children can result in unique adverse events not seen in mature adults.[6] Since adult safety data does not always predict pediatric outcomes, pediatrics may require different dosing and monitoring protocols. Thus, it is essential that children be included early in clinical trials to proactively determine safety and dosing in children.

**Alliance Recommendations:**

- **Given the ethical and scientific imperatives to include children with rare diseases in clinical trials at the outset, we urge the FDA to more explicitly state upfront that this guidance applies to all ages, including pediatric populations.**

[3] FDA. Ethical Considerations for Clinical Investigations of Medical Products Involving Children. Draft Guidance for Industry, Sponsors, and IRBs. (2022 Sept.) P. 10. https://www.fda.gov/media/161740/download
[4] M. Summar, et al. (2025) Rewriting the Safety Script: Including Children Early in Clinical Trials. p. 11. [Unpublished manuscript]
[5] K. O'Hara. (2016 Dec 5) "Paediatric pharmacokinetics and drug doses." Aust Prescriber., vol. 39(6):208–210. https://pmc.ncbi.nlm.nih.gov/articles/PMC5155058/
[6] M. Summar, et al. (2025) Rewriting the Safety Script: Including Children Early in Clinical Trials. p. 3. [Unpublished manuscript]

- **We urge FDA to reference pediatric populations in specific sections throughout the guidance wherever appropriate.**
- **Further, we urge FDA to strongly encourage sponsors to include pediatric protocols in clinical trial designs at initiation and to discuss pediatric protocols in early-stage meetings with FDA.**

## Specific Considerations for Guidance

The Alliance offers the following comments on specific aspects of the draft guidance:

***III. Innovative Clinical Trial Designs***

*P. 3, lines 72-73 "FDA recommend that sponsors discuss options with FDA as early as possible..."*

**Issue:** As mentioned above, if children are not included in a clinical trial design from the beginning, we may never get a pediatric-specific clinical trial because the approved treatment likely will be used in children off-label.[7] If the treatment is not specifically studied in pediatric populations, important safety signals may be missed and dosing or administrative strategies may remain suboptimal . As a consequence, safety issues could be mischaracterized and the true impact of the treatment in children may remain unknown.

Including children at the outset of a clinical trial and incorporating pediatrics in the clinical trial design discussed with FDA in the early stage of development will allow for early data gathering and evidence generation in rare pediatric populations. By including pediatric protocols in the early stage discussions with FDA (and then subsequently, as needed), a sponsor will be better positioned to identify and select the ideal outcome marker, which may be different if a disease manifests differently in younger patients than in older patients.

With rare disease in small populations, there is a very limited universe of possible clinical trial participants. Another reason for including children by not setting arbitrary limitations on the age of enrollment in these clinical trial designs at the early stages is that this allows for increases in the pool of available patients. A greater number of participants can improve the science of and

[7] M. Summar, et al. (2025) Rewriting the Safety Script: Including Children Early in Clinical Trials. p. 8. [Unpublished manuscript]

evidence generated by the clinical trial and account for factors such as higher rates of non-adherence to medication among teens.

**Alliance Recommendation: The Alliance concurs with FDA's recommendation of early engagement with the Agency and urges FDA to go a step further in its recommendation by explicitly encouraging sponsors to include pediatrics in their options for innovative clinical trial designs discussed at the initial development stages with the Agency.**

### *III.A. Single Arm Trials Utilizing Participants as Their Own Control*

*P. 3, lines 77-103*

**Issue:** The Alliance appreciates FDA's inclusion of single arm trials utilizing participants as their own control. We concur that a single arm trial can be helpful when there is a small pool of subjects for a rare disease. In such situations and particularly in progressive diseases, it is often not feasible to impose strict inclusion or exclusion criteria. Patients may enroll at markedly different stages of disease progression, which can diminish the utility of outcome measures designed for the population as a whole. There are also several ethical benefits to single-arm trials, especially in rare diseases, such as incorporating patient preferences and ensuring more equitable treatments. Moreover, single-arm trials have scientific rigor in terms of control (the patient's own baseline) and replication. Other benefits of single-arm trials include shorter clinical trial durations which are less costly.[8]

By including pediatrics in single arm trials, there is a real opportunity to identify and measure data from actual patients in the study at a time that is more relevant to the outcomes for the study. Also in very variable diseases (e.g. congenital myotonic dystrophy) a single-arm trial allows monitoring of change in symptoms that matter to each individual person (e.g. improvement in GI symptoms is very important to some children, but others do not have significant GI issues, but a drug may have meaningful effects on their cognitive function, pain levels, or mobility). Additionally, in children there is also benefit in allowing each person to have their own baseline so that drug effects can be viewed on top of where the child is developmentally at the start of treatment and on the backdrop of their own development. There is also the possibility of getting treatments to pediatric patients sooner and with less cost for the development program. We have already seen how a single-arm trial can be used to successfully obtain approval of treatments for rare pediatric diseases, for

[8] M. Wang, et al. Single-arm clinical trials: design, ethics, principles. (2024 Jun 4) BMJ Support Palliat Care. vol. 15(1). https://pmc.ncbi.nlm.nih.gov/articles/PMC11874317/

example cerliponase alfa for the treatment of CLN2 disease, a rapidly progressive rare pediatric neurodegenerative disorder.[9]

**Alliance Recommendation: Given the importance of using single arm trials in pediatric-focused drug development programs, the Alliance encourages FDA to specifically state on line 80 that this design could be used in cell and gene therapy development programs for small populations including both adults and children.**

### *III.D. Adaptive Clinical Trial Designs*

*P. 5, lines 143-168*

**Issue:** We are excited about adaptive clinical trial designs and believe they offer an achievable pathway to timely approval of treatments for rare pediatric diseases. Adaptive and age-stratified designs offer feasible, safe pathways to generate pediatric safety data earlier, reduce off-label use, and accelerate access to appropriately dosed, evidence-based therapies for children. Adaptive trial designs enable the concurrent enrollment of adults and children in parallel arms, with real-time data monitoring. Rather than waiting years to cascade from one age group to another, these designs allow for dynamic safety assessment and can pause enrollment selectively if adverse signals emerge.[10]

**Alliance Recommendation: The Alliance supports the recommendations outlined in this section, and again urges FDA to explicitly discuss applicability of this design to pediatric study populations. One suggestion would be to add "both adult and pediatric" before "participants" on line 144.**

### III.E. Bayesian Trial Designs

*P. 5-6, lines 172-183*

**Issue:** The Alliance appreciates the specific mention of Bayesian approaches to aid in establishing effectiveness within pediatric populations. However, we are concerned that the guidance states

[9] FDA. Label for BRINEURA (cerliponase alfa). Revised: 04/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761052lbl.pdf. Accessed on 10/31/2025.
[10] M. Summar, et al. (2025) Rewriting the Safety Script: Including Children Early in Clinical Trials. p. 2. [Unpublished manuscript]

that effectiveness must be demonstrated first in adults. Bayesian methods can in some cases be used for pediatric clinical trials without first conducting adult trials, particularly when data are limited.[11] Bayesian methods also allow combining data from adults and pediatrics to determine proper dosing and detect safety signals, as discussed by FDA in a 2022 paper.[12]

**Alliance Recommendation: To allow for greater flexibility for Bayesian trial designs to be used in pediatrics when appropriate without first being used in adults, we recommend on line 178 that FDA modify the sentence to say "…pediatric populations after, or along with when appropriate, effectiveness…"**

**IV.A. Treatment Landscape Considerations**

*p. 6, lines 200-209*

**Issue:**

The Alliance appreciates FDA's acknowledgement that criteria that require patients to have exhausted available therapies may not be appropriate. Similarly, trial designs that require patients to go off current therapies that may be helping manage symptoms or providing some other benefit, so-called "washout periods," can be detrimental to patients' health and often deter participation in a clinical trial. Washout periods often make it difficult if not impossible to complete the trial if they force a person to forgo the known for the unknown. Although there is a rationale for "washout" periods for some cell therapies (e.g. CAR-T) and chemotherapy, in 2021, the National Cancer Institute recommended that washout periods be eliminated for most prior cancer therapy.[13]

Sometimes alternatives are possible. For example, the "overlap model", where there is overlap in dosing down of the current drug while dosing up on the trial drug, could be employed. Other considerations include whether the trial design needs to fit within Subpart D § 50.52[14], the stage of

[11] D. Azzolina. "Navigating challenges in pediatric trial conduct: integrating bayesian sequential design with semiparametric elicitation for handling primary and secondary endpoints" (2025, March 31) BMC Med Res Methodol vol. 25:82. https://pmc.ncbi.nlm.nih.gov/articles/PMC11956446/
[12] J. Travis, et al. "Perspectives on informative Bayesian methods in pediatrics" (2023 Nov 2) J Biopharm Stat vol. 33(6):830-843. https://pubmed.ncbi.nlm.nih.gov/36710384/
[13] National Institutes of Health, National Cancer Institute. Memorandum: Modernizing and Broadening Eligibility Criteria Initiative (2021, Dec. 17). https://dctd.cancer.gov/research/ctep-trials/trial-development/eligibility-initiative.pdf
[14] Subpart D—Additional Safeguards for Children in Clinical Investigations. § 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. (21 CFR § 50.52) https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/subpart-D/section-50.52

the disease for stratifying patients into comparable groups, and titrating patients. The ethics and science of each of these should be strongly considered, discussed early with FDA, and planned for upfront.

**Alliance Recommendation: We would urge FDA to also include language cautioning against "washout periods." This could be done by adding on line 204 "or washout periods" after "therapies."**

### *IV.B. Symptom Status Considerations*

*P. 7, lines 214-223*

**Issue:** We appreciate FDA's recognition that some people may not be symptomatic in early stages of certain genetic diseases, and the recommendation that sponsors consider whether all affected patients will develop symptoms. Even if patients with a rare disease have delayed symptom onset, the disease could still be causing substantial damage to the body. For example, in pediatric patients with Limb-Girdle Muscular Dystrophy, although it depends on the subtype, the typical age of onset of symptoms is between 8 and 15 years old.[15] However, even if a young child with LGMD was asymptomatic, that should not preclude them from eligibility for a clinical trial.[16] Rather, it would be ideal for pediatric patients to receive treatment before a rare disease fully manifests as that would provide the best opportunity to change the trajectory of the disease and significantly improve the child's life possibly through adulthood. Although symptom status endpoints will vary a lot between and within rare diseases, it is important that biomarkers be tested for early even when symptom status will not be the efficacy endpoint in these cases. However, it is unclear what would constitute relevant endpoints with respect to symptoms. For example, people with myotonic dystrophy may show splicing changes prior to symptom onset, which could be measured for a therapeutic effect before motor symptoms are measurable allowing for the possibility that correcting the splicing would prevent the muscle (or cognitive, or GI, or other system) symptoms ever developing.

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[15] Nationwide Children's. Limb-Girdle Muscular Dystrophy. https://www.nationwidechildrens.org/conditions/limb-girdle-muscular-dystrophy Accessed on 11/17/2025.

[16] MP Wicklund, et al. Limb-Girdle Muscular Dystrophy Scientific Workshop. A Multistakeholder Discussion Focused on Charting the Path Forward for Drug Development. (2025, July30) Neurology Clinical Practice. Vol.15, no.5. https://www.neurology.org/doi/10.1212/CPJ.0000000000200496

**Alliance Recommendation: We urge FDA to strengthen the language around what would constitute relevant endpoints and exercise flexibility with regard to demonstrating and providing data on symptom status endpoints.**

***IV.C. Study Population Representativeness***

*P. 7, lines 227 - 255*

**Issue:** In this section, FDA discusses the need for additional safeguards for pediatric clinical trials. However, the discussion does not address the acceptable benefit-risk balance. While safety is important, in many rare pediatric diseases, the benefit-risk calculus is different. Patients and their families may be willing to assume more risk for potential benefits, especially if the alternative is significant morbidity or mortality.

FDA states in the guidance that IRBs must only approve criteria in compliance with 21 CFR parts 50, including § 50.52 regarding direct benefit to children and § 50.53 regarding greater than minimal risk. In both of these, there is naturally an element of subjectivity. It is important for FDA to emphasize to IRBs that in the case of rare pediatric diseases, especially those with early onset and rapid progression, and/or high unmet medical need, and no available treatments, a higher benefit-risk ratio may be justified. In many cases, dosing nothing is doing harm in itself, if the alternative is the possibility of stabilizing or improving symptoms.

IRBs should actively seek information on patient and family perspectives and preferences regarding benefit-risk considerations and apply the maximum degree of flexibility consistent with those views. In doing so, IRBs should be encouraged to consult FDA's draft guidance "Ethical Considerations for Clinical Investigations of Medical Products Involving Children"[17] for additional direction, as well as patient focused drug development (PFDD) meetings and Voice of the Patient Reports. These resources often provide a comprehensive view of the patient and caregiver perspectives and detail how the disease trajectory can impact families over the short and longer term, providing important context to consider as part of earlier intervention for pediatrics.

**Alliance Recommendation: Within the paragraph starting on line 236, we urge FDA to acknowledge and discuss that there may be additional considerations to determine the acceptable benefit-risk balance for rare pediatric diseases, particularly those with early**

[17] FDA. Ethical Considerations for Clinical Investigations of Medical Products Involving Children. Draft Guidance for Industry, Sponsors, and IRBs. (2022 Sept.) https://www.fda.gov/media/161740/download

**onset, rapid progression, and/or high unmet medical need, and for rare pediatric diseases without any approved treatments. Within the context of this discussion, FDA should go further by urging sponsors to engage with patients, families, patient groups, and clinicians to help inform the acceptable benefit-risk balance for a particular treatment development program and being prepared to discuss patient input in early meetings with FDA.**

**Issue:** A number of factors will determine participation rates in a clinical trial, including the potential benefit and risks of the therapy being studied as well as logistical considerations. Early engagement with patients, caregivers, and patient organizations in trial design can help inform patient preferences and improve acceptability and participation.[18] Patient buy-in is a critical factor to the success of clinical trial enrollment.

**Alliance Recommendation: In addition to the important role that patients and caregivers play in informing treatment development, the Alliance recommends FDA add consideration for the roles of patient organizations and patient community with respect to developing endpoints, determining risk-benefit balance, overcoming logistical challenges, and incorporating other important inputs and feedback.**

## Conclusion

Children with rare diseases, particularly those with early onset and progression, deserve timely access to evidence-based therapies that are scientifically developed and tailored to pediatric patients. When the patient population is pediatric, as it is for many rare diseases, children should be the first group studied, not the last. The Alliance believes that pediatric inclusion at the outset is the most effective way to achieve this goal and we appreciate the continued progress in FDA's thinking about pediatric inclusion and pediatric dosing for rare disease clinical trials.[19] Incorporating pediatric inclusion throughout this guidance will further demonstrate FDA's recognition of the importance of innovative and efficient trial designs to meet the urgent need for

[18] Global Genes. "Early and Often: Reimagining patient community engagement to improve clinical trials feasibility" (2025, Jan. 22) https://globalgenes.org/report/announcing-early-and-often-reimagining-patient-community-engagement-to-improve-clinical-trials-feasibility/

[19] S. Usdin. How FDA plans to make room for kids. Biocentury. July 17, 2024. https://www.biocentury.com/article/652989/how-fda-plans-to-make-room-for-kids

safe and effective products to treat serious and severely debilitating diseases in small populations, including children.

The Alliance appreciates FDA's work on this important guidance. We look forward to future discussions with you as you finalize this and other guidance documents that will help ensure children, especially those with rare diseases, are included as early as possible in clinical trials. If you have any questions or would like to discuss this further, please contact Sara Singleton at Sara.Singleton@Leavittpartners.com.

Sincerely,

**Ron Bartek**
Co-Founder, President, Friedreich's Ataxia Research Alliance
Convenor, Pediatric Inclusion Alliance

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