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WHITE PAPER

Practical considerations for cell and gene therapy trials in neonates and young children living with rare diseases

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For neonates, children and their families living with a rare life-altering disease, a cell or gene therapy (CGT) may represent hope for a potentially curative treatment. While several successful outcomes have been noted in clinical trials and a few CGT treatments have reached the market, more promising products are advancing in the pipeline.

Fortrea is currently supporting an exciting Phase I/II gene editing study in an ultra-rare disease involving the prenatal identification of potential participants and subsequent treatment of neonates and infants. This white paper captures some of our insights learned thus far.

From ethical considerations to long-term follow-up, we will address the obstacles faced in CGT trials for neonates and young children and offer practical insights based on our extensive experience. By addressing the ethical, clinical and operational challenges in these trials, we aim to provide actionable guidance for sponsors, patients, caregivers and clinical sites embarked on these complex yet rewarding trials.

Ethical considerations in neonates and early childhood

As with any cell or gene therapy, the treatment can't be reversed or undone once administered. This level of permanence can be concerning when treating a vulnerable population that lacks autonomy, such as neonates, infants or young children, and in the future, potentially even fetuses. Committing to treatment in a clinical trial requires a long-term commitment to a study protocol and may leave the patient ineligible for future clinical trials or approved gene therapy products.

However, a treatment offered in a clinical trial may represent the only option if other alternatives do not exist. Patients and their caregivers must weigh the benefits, such as the possibility of improving quality of life and/or extending one's lifespan, alongside the potential risks.

Often, families must decide whether to participate in a CGT trial in a vulnerable situation where they just received a devastating diagnosis for their child and where there might only be a short window of opportunity for participation. The relationship with the treating physician will be critical to approach them and guide them through this challenging process. As caregivers may not be familiar with CGT, robust training materials in different formats can help families understand the risk-benefit of study participation and facilitate their decision-making process.

Training materials are especially important in situations where the proposed trial might be a first-in-human (FIH) trial, which is relevant in indications where no adult disease exists and children are the first to be treated.

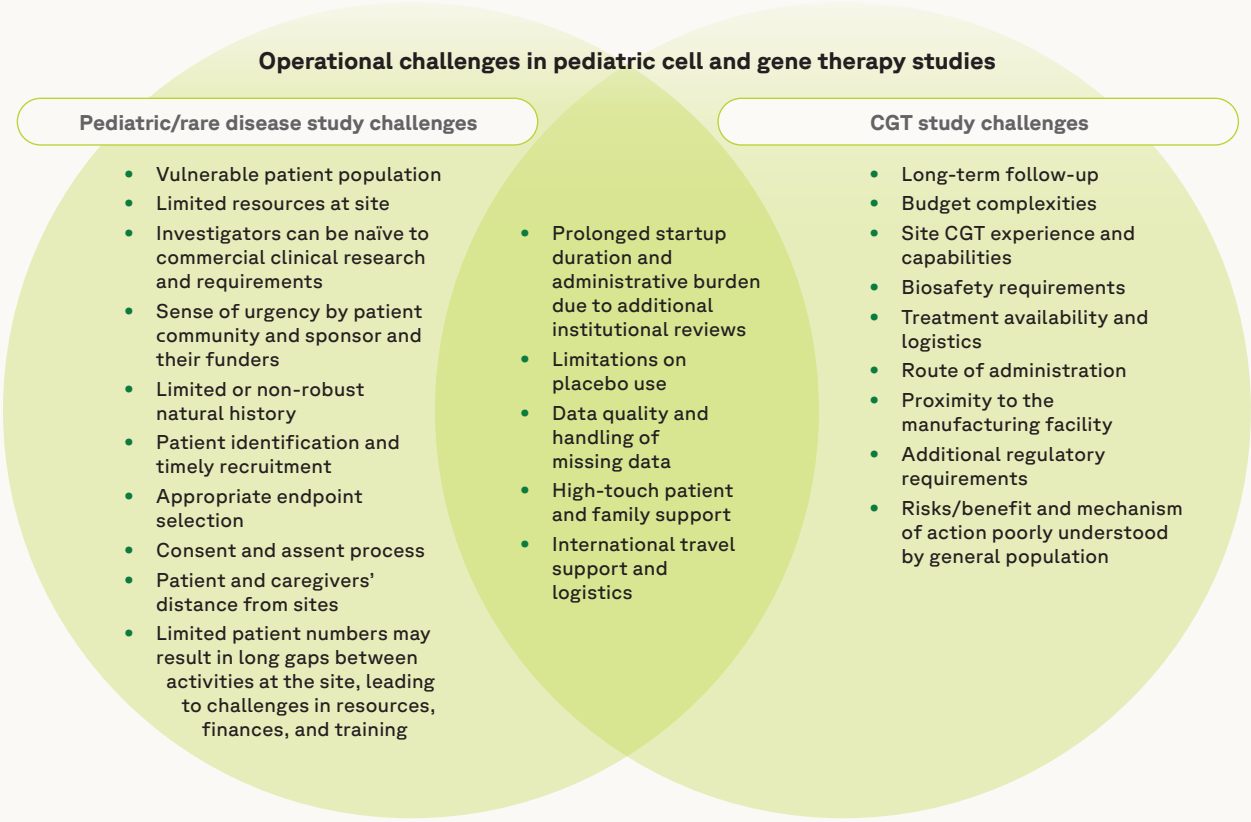
Determining to give CGT products to neonates and young children depends on several factors:

- **Early intervention:** Recent research has shown that outcomes improve with early intervention.[1] The progression of the disease should be considered, which includes the age of onset and the age at which significant medical interventions were utilized in the standard of care. Ideally, therapy would be administered even before the first symptoms of the disease occur, which would require early patient identification, for example, through newborn screening
- **Balancing disease progression and treatment effect:** Potential impacts with the disease progression and the patient's current quality of life also factor into finding the optimal time for dosing, as patients with advanced disease progression may not experience the full benefit of the treatment as compared to those in earlier stages of progression
- **Efficacy of the treatment and LTFU:** The efficacy of the treatment must also be considered but might not be sufficiently characterized, specifically in FIH trials

Important questions include:

Overcoming operational challenges

Pediatric rare disease studies have inherent challenges, as do CGT trials. Together, these challenges can compound, stressing the need for careful planning.



Creating a framework for success: Gathering feedback and creating awareness for pediatric CGT clinical trials

With limited patient populations that may be located around the world, it's important to work with patient advocacy groups, key opinion leaders and research advocates. These groups may be able to help review protocols, provide feedback on the patient and caregiver burden, make suggestions about meaningful endpoints and also provide support materials to families. Presentations sharing preclinical or early clinical data can greatly help generate awareness, increase viability and build interest in a trial.

Early vendor selection and engagement, along with planning sessions, are also essential for supporting international patients. A mock patient/family journey mapping exercise can also help sponsors and sites understand and evaluate each step of the journey from the participants' perspective.

Supporting families

Several considerations can help support families in a pediatric CGT trial.

- **Informed consent and support materials:** To support informed consent, the intricacies of a cell or gene therapy must be explained to patients' families in lay terms with a clear description of the procedure, risks and benefits. Study materials must explain how the treatment is intended to work in the context of a specific disease and should be designed to "grow with the child" as they age to match their developmental stage and provide education to support the assent process
- **International support:** Some families may travel internationally to participate in a CGT trial. In these cases, it might be necessary to establish eligibility before the patient travels to the site. Local regulatory/ethics requirements should be reviewed to ensure participation can be supported. The families should clearly understand the duration of their stay, the number of caregivers that can be accommodated and the requirements for travel documents. Families should also have a plan for their insurance and finances, assuming they need to take leave from their work and may need medical care coverage outside of their home country

  At the clinical site, the families benefit from practical resources like housing assistance, local guides and access to basic amenities like food, communication tools and emotional support networks. The more information, advice and support that a sponsor can provide, the lower the burden on the family
- **Long-term follow-up:** Families must also understand the lifetime commitment required to fulfill long-term follow-up requirements and how the timing may impact their decision-making. When the therapy works as intended, study participants may lose motivation to keep up with the study. To collect long-term safety and efficacy data, sponsors need to ensure that participants remain interested in the study as they age. The LTFU study should be designed to make it as easy as possible for the patient and their family to continue to participate over the very long term, following the standard of care as closely as possible and using real-world evidence where appropriate
- **Planning for change:** Understanding that families may relocate and live far away from the original study site, sponsors may offer a hub and spoke model, where a patient would still be associated with their original site but would complete any future visits with their local care team to reduce the travel burden on the family

Site feasibility

Building relationships and maintaining rapport with sites—before a trial starts—is essential. Sponsors can share their preclinical and early clinical data to keep sites apprised and engaged during the process, ask for feedback on study design and learn what sites need to make a trial successful.

While a thorough assessment of each site helps create a baseline and optimize selection, it is a challenging process. However, with ample time to fully vet sites, sponsors can define their "ideal" site based on the available population, understand a site's interest and experience with the indication and/or cell and gene therapies along with their willingness to be trained. Study-specific training, equipment, support and biosafety level (BSL) requirements may also be a factor for certain trials.

It's important to note that experienced CGT pediatric sites may be in high demand, especially in those experienced with a rare disease, stressing the need to find and train new sites ahead of time.

Supporting the site during pre-activation

Once a site is selected, the activation pathway can be complex. Early virtual kickoff meetings can identify all committees and departments that need approvals, and the team can create a detailed path to activation. Frequent check-ins are essential to understand if needs are being supported, monitor progress and develop a flexible communication plan that covers multiple scenarios.

Transparency between the sponsor, CRO and site can help build strong partnerships as updates are provided, such as any new preclinical or early clinical data, progress with regulatory authorities along with current and upcoming milestones for both the study and the site. Sites must also understand the treatment's safety profile and be invited to ask questions to ensure a clear understanding of the trial and its objectives.

Ongoing support to reduce burdens

From the site initiation visit (SIV) onward, sites should continue to feel supported. Comprehensive training must cover several aspects, such as drug preparation complexities, drug administration compliance, safe handling precautions, safety and tolerability parameters, mock visit/drug prep walkthroughs and plans for turnover.

Site support also involves support for the families to help minimize the site burden. Specific vendors can be engaged to support home health services and other patient support vendors specialize in logistics to help with travel, visas, temporary housing, access to schooling and pet and/or sibling care. If applicable, it is helpful to select vendors who are familiar with the unique needs of rare disease patients.

Clinical research associates (CRAs) and the sponsor should feel connected to enable real-time availability and provide rapid resolution to any questions. CRAs benefit from refresher training and CROs should have CRA turnover/succession plans to ensure seamless continuity throughout the trial.

Finally, frequent knowledge sharing and updates can also help build a sense of community between the sites, CRO and sponsors and strengthen the collaboration between multidisciplinary teams.

Looking ahead

Cell or gene therapy clinical trials are inherently challenging and the complexities of working with a vulnerable pediatric population intensify these efforts. Successful trials involve careful planning and a robust approach to meet the needs of patients and caregivers, as well as investments in strong site relationships to reduce burden. While CGT trials promise hope to patients, families and their communities for a potential cure, each step forward can also contribute to advancing research, better treatment options and improved patient outcomes to help address unmet medical needs for neonates and young children living with rare life-altering diseases.

References

1. Thakar MS, Logan BR, Puck JM, et al. Measuring the effect of newborn screening on survival after haematopoietic cell transplantation for severe combined immunodeficiency: a 36-year longitudinal study from the Primary Immune Deficiency Treatment Consortium. *Lancet.* 2023 Jul 8; 402(10396):129-140.

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