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REVIEW ARTICLE

Ethical challenges for a new generation of early-phase pediatric gene therapy trials

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After decades of setbacks, gene therapy (GT) is experiencing major breakthroughs. Five GTs have received US regulatory approval since 2017, and over 900 others are currently in development. Many of these GTs target rare pediatric diseases that are severely life-limiting, given a lack of effective treatments. As these GTs enter early-phase clinical trials, specific ethical challenges remain unresolved in three domains: evaluating risks and potential benefits, selecting participants fairly, and engaging with patient communities. Drawing on our experience as clinical investigators, basic scientists, and bioethicists involved in a first-in-human GT trial for an ultrarare pediatric disease, we analyze these ethical challenges and offer points to consider for future GT trials.

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INTRODUCTION

In 2015, the US National Institutes of Health (NIH) launched a first-in-human gene therapy trial for giant axonal neuropathy (GAN)—an ultrarare childhood condition characterized by progressive motor decline and eventual death. The trial was eagerly awaited, and in part instigated, by the GAN community. Preclinical research suggested that the investigational gene therapy (GT; used without intending to imply a therapeutic effect) might slow or halt disease progression—a unique prospect for GAN, given the lack of available treatments beyond supportive care.

Despite (and because of) its promise, the GAN GT trial has faced pressing ethical challenges that complicate the translation of pediatric GT, particularly for the many rare diseases with severe effects and limited treatment options. For example, when is there enough preclinical evidence to begin an early-phase trial? How should doses be selected? Which interested families should have the opportunity to enroll a child? And how should a patient community, especially when it plays an essential role in launching a trial, be involved in answering such questions?

The GAN trial offers a starting point for analyzing these challenges at a time when, after decades of setbacks [1], a new generation of GT trials is starting to produce major breakthroughs. The first five GTs have received US Food and Drug Administration (FDA) approval since 2017 [2, 3], all of which involve "the introduction, removal, or change in the content of a person's genetic code with the goal of treating or curing disease" [4]. Two approved GTs, similar to the GAN GT, deliver genetic material to patients' cells in vivo using adeno-associated viruses (AAVs) [5]. Other approved or investigational GTs span in vivo and ex vivo approaches, including viral-mediated gene replacement, genetically modified cell therapy, and gene editing [1]. While the GAN trial is most similar to other in vivo viral-mediated GT trials, the above ethical challenges will also apply to GT trials testing other approaches.

The current research landscape suggests that many GTs will mirror the GAN trial's ethical complexity when they enter first-in-human testing (Fig. 1). Over a third of the 900 GTs in development target rare diseases [2, 6], many of which are genetic [7], pediatric-onset [7], and life-limiting [8], and nearly all of which lack an FDA-approved treatment beyond supportive care [9]. This foreshadows an ethically challenging mix for early-phase (i.e., phase 1 and 2) GT trials: (1) children with serious conditions and limited treatment options; (2) experimental interventions that may therefore be viewed as the best available options, but which remain uncertain in their risks and potential benefits; and (3) given small patient numbers, low commercial interest that may cause patient communities to become active [10, 11] in shaping and/or funding research. Specific classes of GT can introduce additional and unique ethical complexities. For example, in vivo AAV-mediated GTs are irreversible and therefore cannot be withdrawn once administered. They also cause participants to develop antibodies to the viral vector used in the intervention [12]. These GTs thus pose an important risk: they currently make trial participants ineligible for future (potentially more therapeutic) doses of any GT involving the same vector.

Despite a substantial literature on the ethics of early-phase research [13–15] and GT research specifically [16–18], some ethical challenges raised by the above combination of factors (e.g., dose selection) remain unresolved, and require further elaboration in the pediatric GT context. Others (e.g., how to select participants fairly when there are fewer trial slots than eligible and interested patients) are comparatively underexplored, meaning little guidance is available. Considering the many GTs approaching early-phase testing [6] and the importance of preserving trust as the field expands, all of these challenges are increasingly urgent to address.

This paper analyzes central ethical challenges raised by early-phase pediatric GT trials in three domains: risk–benefit evaluation, fair participant selection, and engagement with the patient community. Drawing on our experience as clinical investigators, basic scientists, and bioethicists involved in the GAN trial, and on the available literature, we offer points to consider for

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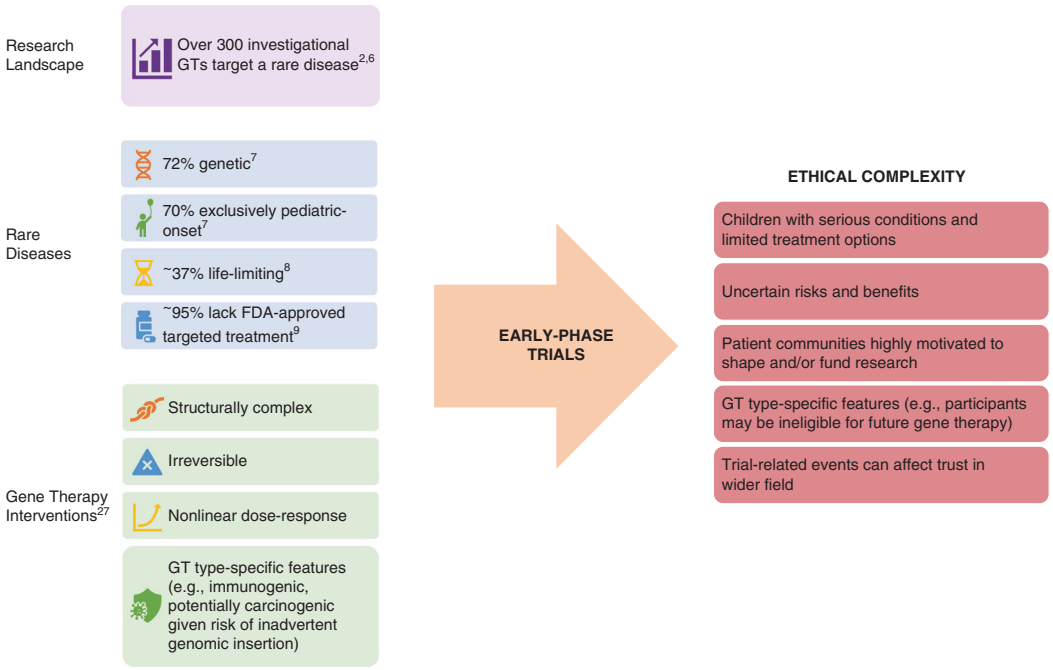

Fig. 1 Ethical complexity in early-phase pediatric gene therapy (GT) trials. This figure highlights ethical issues analyzed in this paper and as such is not exhaustive.

investigators, sponsors, institutional review boards (IRBs), and others. With this analysis, we hope to inform the design and conduct of these important trials.

THE GIANT AXONAL NEUROPATHY GT TRIAL

GAN is caused by recessive, loss-of-function variants in the *GAN* gene, which encodes gigaxonin, a ubiquitiously expressed protein that is particularly critical for neuronal structure and function. The condition has been reported in just 83 individuals worldwide (50 families; 50 unique pathogenic variants) [19], and about 70 patients are presently known to the GAN study team. Children with typical GAN experience mild sensory loss and motor weakness beginning in early childhood, with progressive neurodegeneration, central nervous system involvement, and eventual respiratory failure. No treatments currently exist beyond careful supportive care, and patients typically do not survive beyond the second or third decade [20].

The GAN GT trial (NCT02362438) is an ongoing phase I, nonrandomized, open-label, first-in-human, dose escalation study. Like most early-phase GT trials, the trial investigates the safety and tolerability of GT at increasing dose levels. A secondary goal is to collect initial data about the GT's efficacy in slowing and potentially halting the inexorable progression of GAN.

Preclinical vector development and later clinical lot production began over 10 years ago, instigated and funded in part by Hannah's Hope Fund (HHF), a "public charity…to support the development of treatments and a cure for GAN [21]." The GT attempts to deliver an intact and codon-optimized complementary DNA (cDNA) copy of the *GAN* transcript to the nervous system using an adeno-associated virus 9 (AAV9) vector, administered into the cerebrospinal fluid via lumbar puncture [22]. The GAN trial is novel for administering AAV-mediated GT using an intrathecal delivery route. Thus far, 14 participants (ages 6–14 years at enrollment) from around the world have been enrolled at one of four dose levels.

The GAN trial has been conceived and conducted in close coordination with the GAN community (notably HHF, parents of children with GAN, and several more mature children with GAN); the National Institute of Neurological Disorders and Stroke Clinical Trials Unit; an NIH IRB, Institutional Biosafety Committee (IBC), and data safety monitoring board (DSMB); the Recombinant DNA Advisory Committee (RAC); the FDA; and the NIH Clinical Center Bioethics Consultation Service. Moreover, ongoing collaboration with the scientists who developed the GT has allowed for protocol modifications in response to emerging preclinical research.

UNRESOLVED ETHICAL CHALLENGES IN EARLY-PHASE PEDIATRIC GT TRIALS

In what follows, we analyze ethical challenges in three domains—risk–benefit evaluation, fair participant selection, and engagement with the patient community—that have been particularly pressing in the GAN trial. Other important ethical issues in early-phase pediatric GT trials (e.g., informed consent and assent), including issues beyond trial design and conduct (e.g., which GTs to prioritize for clinical development), will need to be addressed elsewhere.

Evaluating risks and potential benefits

The central goal of clinical research is to produce knowledge that can be used to promote the health of future patients (i.e., knowledge with *scientific and social value*) [23, 24]. Trials may or may not also benefit individual participants. In this context, it is critical to ensure that research risks faced by trial participants are reasonable in relation to the value of the knowledge gained, and any potential benefits for participants themselves [23, 25]. The GAN trial offers insights into two unresolved questions regarding risk–benefit evaluation in early-phase pediatric GT trials.

When is there enough preclinical evidence to begin clinical trials?. The decision to begin an early-phase GT trial—particularly a first-in-human trial—should be based on convincing evidence that a GT could ultimately improve health in patients. Additionally, in pediatric trials, risks above a certain threshold (more than a minor increase over minimal, under US regulations [26]) must typically be justified by potential clinical benefits for participating children (please see Supplementary Box 1 for how nonclinical benefits

Table 1. Determining whether to initiate early-phase gene therapy (GT) trials.

Step	Guiding question	Assessment
1. Form preliminary expectation for GT's risk–benefit profile	What is the study intervention's expected risk–benefit profile for participants?	• Determine the type, magnitude, and likelihood of harms and benefits observed in preclinical studies • Evaluate the balance of benefits and harms
2. Gauge uncertainty in the GT's risk–benefit profile by evaluating preclinical evidence quality	Do preclinical studies support a causal relationship between the GT and observed outcomes (internal validity)?	• Check whether design features support a causal relationship (e.g., controls, randomization, blinding)
	Do preclinical studies accurately represent the clinical conditions in which the GT will be tested (construct validity)?	• Look for similarity between preclinical models and human patients (e.g., clinical presentation, age- and sex-matching for animal models) • Check whether preclinical GT was delivered in an analogous way to the intended delivery in humans (e.g., same volume-adjusted dose between animals and humans)
	How generalizable are preclinical results (external validity)?	• Determine whether preclinical safety and efficacy findings have been validated in multiple models and/or species
	Overall, what is the uncertainty in the risk–benefit profile?	• Judge overall preclinical study quality (internal, construct, and external validity): the higher the quality, the lower the uncertainty
3. Refine judgment of the GT's expected risk–benefit profile by considering evidence on similar GTs	Can data on similar interventions refine or complement the above estimates about harms, benefits, and uncertainty?	• Consider whether similar interventions (e.g., similar vectors and/or delivery routes) have demonstrated safety and efficacy: the more therapeutic and better-characterized any similar interventions, the lower the uncertainty surrounding a favorable risk–benefit judgment
4. Evaluate whether contextual factors influence the ethical acceptability of initiating early-phase trials	Do contextual factors suggest that it is more or less acceptable to begin early-phase trials?	• Evaluate relevant contextual factors: the more serious and rapidly progressive the disease, the more limited the alternatives, and the higher the support by the patient community, the more acceptable early-phase trial initiation may be
5. Judge whether initiating early-phase trials is ethically justified	Is it ethically acceptable to begin early-phase trials in the target population?	• Make all-things-considered judgment, given the GT's expected risk–benefit profile, its associated uncertainty, and relevant contextual factors

This process synthesizes and builds on existing guidance for preclinical study design and early-phase trial initiation [13, 29–32]. It provides a starting point for investigators, sponsors, IRBs, and regulators when determining whether an investigational GT's risk–benefit profile is sufficiently favorable, and its associated uncertainty sufficiently low, to initiate early-phase trials.

and/or a trial's scientific and social value could factor into this analysis) [23, 25]. At the same time, any early-phase trial involves uncertainty in the type, magnitude, and likelihood of the experimental intervention's harms and benefits, as well as the intervention's optimal dose, target population (in terms of genotype, clinical manifestations, and age), and cointerventions [15]. GT trials tend to involve particularly high risk–benefit uncertainty, as GTs are structurally complex, can exhibit nonlinear dose–response relationships, and may induce irreversible physiological changes as well as immune-based toxicity (as for in vivo AAV-mediated GT) [17, 27]. In the GAN trial, the novel intrathecal administration route for AAV-mediated GT further increased uncertainty. Before exposing participants to risk, it is therefore essential to judge whether a GT has clinical promise based on preclinical studies, and whether the uncertainty surrounding this judgment is sufficiently low to warrant a clinical trial.

Investigators, IRBs, sponsors, and regulators should evaluate an investigational GT's risk–benefit profile in a systematic and evidence-based way, accounting for its associated uncertainty [23, 28]. To start, this requires forming a preliminary expectation for the GT's balance of benefits and harms based on preclinical evidence, including from cells, small animal models, and/or large animal models when available (Table 1, step 1) [28, 29]. Evaluating the quality of this evidence can then help assess the degree of uncertainty before a trial is launched: higher-quality preclinical studies (i.e., those with strong internal, construct, and external validity) have higher predictive value and thus reduce uncertainty (Table 1, step 2) [13, 29–32]. Considering evidence on similar interventions, such as the translation rate of GTs involving similar vectors, can provide further insight into whether preclinical findings are likely to generalize to humans (Table 1, step 3) [13, 29]. Importantly, relying on this "reference-class" evidence may be essential in the context of GT for rare diseases, given the practical challenge of developing animal models for all 4,000 known rare monogenic disorders [33]. For example, in cases where reasonable efforts (as judged by investigators, sponsors, IRBs, and regulators) fail to develop an animal model that sufficiently reflects the human disease, investigators might instead need to rely on preclinical efficacy studies in patient-derived cells, coupled with evidence from different GTs that target the same organ system using similar vectors and/or delivery routes. This is particularly relevant for trials testing emerging platform-based GT approaches—where different disease-specific transgenes can be delivered using a common vector "platform" [33]—in which investigators can draw on preclinical and clinical evidence gathered across the platform.

In the GAN trial, preclinical studies [22] suggested an overall favorable risk–benefit profile, with resolution of disease pathology in GAN patient fibroblast studies, significant motor and pathological improvement in mouse studies, and no observed adverse

events in mouse, rat, or nonhuman primate toxicology studies. Yet the degree of risk–benefit uncertainty was notable. Preclinical studies supported a causal relationship between the GT and its observed outcomes given appropriate experimental controls, blinded outcome assessment, and other markers of internal validity. However, despite apparent genotype matching to human GAN patients, a knockout mouse model of GAN exhibited milder motor deficits than those observed in humans (limited construct validity, as with many rodent models of human disease). Moreover, while vector biodistribution and pharmacokinetic findings generalized from rodents to nonhuman primates, it was unclear whether other aspects of the GT (e.g., immunogenicity) would be equally generalizable (mixed external validity). Taken together, all of these unknowns—coupled with the novel intrathecal administration of AAV-mediated GT—made the translation of these findings to humans uncertain.

Once the anticipated risk–benefit profile of a GT has been estimated, contextual factors may influence the judgment about whether clinical trial initiation is ethically justified (Table 1, steps 4–5). In the GAN trial, several such factors suggested to the study team, sponsors, IRB, RAC, and FDA that the notable degree of risk–benefit uncertainty was ethically acceptable. In particular, the lack of effective treatments beyond supportive care for a severe, neurodegenerative, and ultimately fatal disease in young children seemed to favor initiating the trial—especially since additional preclinical research was limited by available animal models and could have introduced significant delays, no other disease-modifying treatments were in development, and the patient community itself supported proceeding with a clinical trial.

Given a different set of contextual factors—for example, in cases where the medical need is less pronounced, or where the patient and/or scientific community collectively favor a higher degree of certainty before beginning a trial—additional preclinical research may be preferable. The process outlined in Table 1, which synthesizes and builds on existing guidance [13, 29–32], provides a starting point for investigators, sponsors, IRBs, and regulators when determining whether an investigational GT's risk–benefit profile is sufficiently favorable, and its associated uncertainty sufficiently low, to initiate early-phase trials.

How should risks and benefits be balanced in dose selection?. Reducing risks and enhancing potential benefits for participants are ethical imperatives in all clinical trials [23, 25]. However, these goals can conflict when making certain decisions about early-phase GT trial design. One key set of these decisions includes starting dose selection and subsequent dose escalation.

Some ethicists have proposed that for trials with highly uncertain risk–benefit profiles, more emphasis should be placed on reducing risks to participants through a low starting dose and a cautious dose escalation scheme, even when this might decrease participants' prospect of clinical benefit [13, 34, 35]. In line with this reasoning, the IRB, RAC, and FDA mandated a cautious starting dose in the GAN trial, set fourfold below a level (when scaled to humans) that produced no adverse events in nonhuman primates, and tenfold below a level that produced no adverse events in rats. (These specific thresholds are not necessarily generalizable across trials, as they will depend on the disease, the type of GT, GT-specific features, and the level of risk tolerance given the state of the field and any available therapeutic alternatives.) At the same time, investigators selected a starting dose that was thought to hold a prospect of limited clinical benefit, as recommended by the FDA [28]. Subsequent doses have been escalated gradually—despite preclinical evidence of higher efficacy at higher doses—to reduce the risk of dose-related toxicity in a larger number of participants.

Yet an emphasis on reducing risk in dose selection can also reduce potential benefits for participating children. For one, cautious dosing schemes may increase the chance of delivering subtherapeutic GT doses. More generally, these dosing schemes may limit the number of participants who receive potentially therapeutic doses, and/or the magnitude of any therapeutic effects [35, 36].

Tradeoffs between reducing risks and enhancing potential benefits are inherent to many dose-finding studies, but they can be especially challenging for in vivo viral-mediated GT trials, given the current "one-shot" nature of these GTs. In particular, low and even subtherapeutic GT doses (at present) confer vector-induced immunity, meaning they preclude trial participants from receiving future GTs involving the same vector [12]. This affects the risk–benefit profile of a trial: with a lower prospect of direct clinical benefit, risks to participating children—including the opportunity cost of being ineligible for future GTs—may be difficult to justify (see also Supplementary Box 1). In trials where vector immunity would prevent GT readministration, designs that enhance potential benefits for participants (e.g., higher starting dose, more rapid dose escalation) might therefore be ethically preferable, at least until currently experimental efforts to enable GT readministration by mitigating vector immunity [37] become viable. The case for such designs may be especially strong in GT trials with higher expected safety—for example, because of prior use of a similar vector, dose, or administration route without serious adverse events [36].

Importantly, when surveyed about these ethical tradeoffs in early-phase GT trials, some patient communities support enhancing benefits over reducing risks in dose selection. In one survey [38], the majority of adults with Duchenne muscular dystrophy and caregivers of children with Duchenne cared most about their own or their child's potential to benefit from the trial, while expressing strong concerns that participation might preclude a future GT. In contrast, respondents placed less emphasis on risks including death and long-term hospitalization. Ultimately, choices about dose selection and escalation must satisfy scientific and regulatory criteria based on preclinical data and growing knowledge from the field. Within these constraints, investigators might also engage with the patient community in their trial [39], as well as other trial stakeholders—including the IRB, DSMB, regulators, and preclinical collaborators—to make explicit and well-justified dosing decisions.

Regardless of how risks and benefits are balanced in dose selection, investigators should implement risk-reduction measures that do *not* reduce potential benefits wherever possible. For instance, investigators should adapt study protocols to reduce risks (e.g., the GAN study team implemented a novel steroid regimen to limit inflammatory responses to the AAV vector and transgene) and adhere to halting criteria guided by trial-related adverse events [28]. Investigators should also discuss the risks and potential benefits of the chosen dose during the informed consent process, in addition to emphasizing any unique risks of the GT, such as irreversibility or the inability for readministration. These discussions should involve children themselves, as appropriate given their maturity and degree of comprehension and appreciation, with a view to obtaining assent and respecting dissent. Revisiting these issues on multiple occasions before GT administration may improve understanding by participants and families. It may also help mitigate regret about any adverse outcomes or opportunity costs that result from trial participation, such as the inability to participate in other GT trials.

Selecting participants fairly

Fair participant selection requires that participants are recruited, as well as included or excluded, based primarily on a trial's scientific objectives [23, 25]. In addition, the risks, burdens, and potential benefits of research participation should be distributed fairly across individuals and societal groups [23, 25]. Given the potentially high risks of GT, early-phase trials will generally enroll

patients rather than healthy volunteers [40]. The GAN trial offers insights into two resulting unresolved challenges surrounding fair participant selection in early-phase pediatric GT trials.

Should trials target patients with earlier- or later-stage disease?. Beyond dose selection, a trial's risk–benefit profile can be improved by enrolling participants who might benefit more, or risk less, from the GT [23, 40]. In GT trials for progressive diseases, choosing a study population can be challenging, as the risks and potential benefits of GT may differ depending on a participant's stage of disease [40, 41]. For example, the GAN GT—like all existing GTs for neurodegenerative conditions involving irreversible tissue damage—has the potential to slow or halt disease progression but not restore damaged tissues. This means that patients with early-stage disease might benefit more from trial participation than patients with more advanced disease, who may be outside a window of therapeutic opportunity [42]. At the same time, patients with earlier-stage disease, while less prone to some procedure- and disease-related complications, are at risk of losing more quality of life or life-years in case of adverse events. Investigators therefore face complex tradeoffs between reducing risks and enhancing potential benefits when designing a trial's eligibility criteria, or when selecting among eligible patients if demand for participation exceeds enrollment capacity.

Commentators have debated whether to target patients with earlier- or later-stage disease in various research contexts [43, 44], including GT trials [17, 39, 45, 46]. Reasons to target patients with earlier-stage disease can include their higher prospect of benefiting from some GTs, and their ability to better tolerate mild or moderate side effects [39, 43]. There may also be scientific and social value in enrolling patients with earlier-stage disease. First, insofar as they are more likely to benefit from the GT, their inclusion increases the likelihood of detecting a potential efficacy signal (which may provide necessary momentum and funding for continuing the research) [17, 39, 43, 44]. Second, they are at lower risk of disease-related complications and death, making it easier to attribute adverse events to the GT rather than the underlying disease.

In contrast, targeting patients with later-stage disease can offer other advantages. For one, these patients stand to lose less quality of life or fewer life-years from serious adverse events [35, 45, 46]. Trial enrollment may also represent an "only chance" for these patients who may soon become ineligible, whereas patients with earlier-stage disease may have future opportunities to receive the current, or another, investigational or approved therapy. Finally, patients with advanced disease may be older and have gained more experience with their condition—factors that can enhance their ability to provide assent or consent to trial participation.

Choices regarding who to target for enrollment in early-phase GT trials, like those regarding dose selection, ultimately require making context-specific ethical judgments that incorporate scientific and clinical considerations. Investigators might consider two strategies for doing so. First, consulting stakeholders such as IRBs and regulators can help keep trials responsive to scientific and regulatory requirements, and engaging members of the patient community may help investigators to promote patients' and families' preferences and values in participant selection [39, 45]. For example, as described above, some patient communities may be more tolerant of risks that arise from enrolling patients with early-stage disease, given these patients' higher prospect of benefit [38].

Second, dosing participants in sequence rather than in parallel can allow investigators to adjust their strategy for selecting participants as the trial context changes [28]. For example, in the early stages of the GAN trial—when uncertainty about the risks and potential benefits of the GT was highest—investigators targeted patients with more advanced disease (as discussed with the IRB, RAC, and FDA) to prevent potential serious adverse events from affecting patients with more remaining quality of life or life-years. When these participants did not experience serious harms related to the GT, investigators began to target patients with earlier-stage disease.

Because enrolling patients at different disease stages will make a trial's cohort more heterogeneous, investigators should consider potential disadvantages for data interpretation and ways to mitigate them. In the GAN trial, the fact that participants had previously been enrolled in a natural history study allowed for comparison of each participant's pre- and post-GT rate of disease progression, in addition to comparison with the average progression rate (which, for GAN, does not vary with disease stage); this has mitigated concerns about comparing trial outcomes across participants. Investigators should also consider any trial delays resulting from sequential enrollment that, if significant, could disfavor such a strategy.

How should participants be selected in high-demand GT trials?. As mentioned above, the GAN trial has brought together a combination of factors that other pediatric GT trials will likely share: a serious disease with limited treatment options, the perceived therapeutic promise of GT, and a well-organized patient community that has improved recruitment. As a result, the number of eligible and interested patients for the GAN trial has consistently exceeded the available slots. The challenge of allocating limited enrollment slots in what might be called a "high-demand trial" remains underexplored [47], likely because accruing enough participants is the more common problem in clinical trials, including for rare diseases [48]. Yet high-demand trials do occur, particularly when a trial offers perceived health-related, psychological, or other benefits that motivate many people to seek participation [47, 49, 50].

How should investigators in high-demand GT trials allocate limited enrollment slots? Defining a clear strategy is important to avoid ad hoc and potentially biased decisions. In early-phase GT trials, any such strategy can affect three ethical dimensions of a trial: scientific and social value, the risk–benefit profile for participants, and justice (Table 2) [51]. Participant selection strategies tend to optimize one or two of these ethical dimensions but may involve tradeoffs with others. For example, as mentioned above, the GAN study team has recently prioritized eligible patients with earlier-stage disease to enhance potential clinical benefits for participants as well as the trial's social and scientific value. Yet this strategy has not given all eligible patients an equal chance to participate in the trial, thus conflicting with notions of justice that focus on equal chances, or on priority for patients with later-stage disease who may have limited time for other treatment options to become available.

There is no universally preferred strategy for allocating limited enrollment slots in high-demand GT trials, as participant selection priorities will depend heavily on a trial's context [47, 51]. As described above, investigators in the GAN trial have targeted different patient groups (i.e., earlier- vs. later-stage disease) based on whether the top priority has been reducing risks, enhancing potential benefits, or enhancing the trial's scientific and social value as the trial has progressed. As a secondary consideration throughout the trial, when eligible patients have presented within a similar stage of GAN, investigators have prioritized patients with the fastest-progressing disease, for whom the trial may have represented the last chance to participate in potentially beneficial research. This has been an attempt to give these patients a more "equal cumulative chance" to participate in the GAN trial—one conception of justice in participant selection (Table 2).

The GAN study team has deliberately avoided introducing additional criteria for allocating trial slots, given a lack of consensus among the study team and research ethicists surrounding such criteria. For example, the investigators initially considered prioritizing siblings of earlier trial participants as a way

Table 2. Ethical considerations for selecting among eligible patients in high-demand gene therapy (GT) trials.

Ethical consideration	Potential implementation	Illustrative example(s)
Enhance scientific and social value	Increase representativeness to improve generalizability	• Prioritize eligible patients whose inclusion would improve the representation of relevant genotypes (e.g., variants) or other characteristics (e.g., sex, race, age, comorbidities)
	Increase knowledge about clinically relevant subgroups	• Prioritize—and potentially overrepresent—eligible patients with clinically relevant genotypes (e.g., variants) or other characteristics (e.g., sex, race, age, comorbidities) • Prioritize—and potentially overrepresent—eligible patients in whom the potential effects of the GT are more likely to be observable
Enhance risk–benefit profile for individual participants	Enhance potential benefits	• For neurodegenerative or similar diseases, prioritize eligible patients with earlier-stage disease if GT has the potential to halt disease progression, but not to restore affected tissues
	Reduce risks	• Prioritize eligible patients expected to better tolerate side effects or complications of GT • Prioritize eligible patients with advanced disease who would lose less quality of life or fewer life-years from adverse events • Prioritize eligible patients with reliable local health care and ability to maintain follow-up for GT safety
Promote justice	Provide equal chances	• Give all eligible participants an equal chance of participating in the trial
	Promote equal access	• Ensure that eligible patients with unreliable local health-care access (e.g., because of country of residence or lack of health-care insurance) receive an equal opportunity to participate
	Prioritize disadvantaged groups	• Prioritize eligible patients with the most limited treatment or research options • Prioritize eligible patients from otherwise disadvantaged groups
	Promote reciprocity	• Prioritize eligible patients who participated in preparatory research for the GT trial (e.g., natural history study)

Participant selection approaches generally optimize one or two of these considerations and may involve tradeoffs with others (e.g., promoting equal opportunity to enroll may conflict with reducing risks to participants). Different implementations of the same consideration (e.g., enhance potential benefits and reduce risks) may also conflict. The preferred approach will depend on the specifics of the trial and may affect a trial's number of participants, location(s), cost, and other features. This framework builds on a previous analysis of high-demand trials [51].

to recognize families' past contributions to research and promote equality within families. However, they ultimately did not implement such a strategy, since it would also have (potentially unfairly) placed disproportionate risks and burdens on families with multiple enrolled children.

Investigators in other high-demand GT trials should carefully consider which ethical dimensions to prioritize given the specifics of their trials, and thus which participant selection strategies to pursue. For example, investigators in later-phase trials testing well-characterized GTs might have strong reasons to select participants who will benefit most [52]. As the GAN trial highlights, multiple ethical dimensions can be important within a single trial, and a trial's scientific and social context may change as investigators gain additional knowledge about the GT or the broader field. As with other challenges related to trial design, engaging with the patient community may help clarify their preferences and values—another important part of a trial's context. Regular review and revision of a trial's participant selection approach can help ensure that this approach remains current.

Engaging with patient communities

Engaging the patient community in the planning and conduct of clinical trials can be important as a matter of respect [53]. It may also make trials more responsive to patients' and caregivers' preferences and values, and more feasible to implement [54]. The GAN trial provides insights into two associated challenges that investigators in other early-phase pediatric GT trials may also face.

How should investigators engage with highly invested patient communities?. Given the limited commercial interest in developing therapeutics for many rare diseases, rare disease communities may be especially involved in shaping GT research [10, 11, 55, 56]. Indeed, the parent-founded organization HHF led efforts to advocate for research, mobilize funds, facilitate scientific collaborations to drive preclinical development of the GAN GT, and improve recruitment by informing families about the trial. Such major time, intellectual, emotional, and—in some cases—financial investments raise the questions of whether, and how, to tailor patient engagement strategies to highly invested patient communities that may be involved in early-phase pediatric GT trials.

Considering their previous involvement in shaping research, highly invested patient communities may be especially knowledgeable about a disease, the experience of having a disease, patient and family preferences related to trial design (e.g., meaningful outcome measures), and other useful topics for enhancing the value of a trial. They may also be eager to provide input and well-positioned to facilitate the relationship between investigators and the larger patient community (e.g., by helping investigators identify potential participants). Thus, investigators might consider particularly close engagement with highly invested patient communities, given the value such engagement may hold for improving trial design and recruitment. At the same time, conflicts of interest may arise when members of highly invested patient communities become engaged in research. For example, parents' views on trial initiation, participant selection, and other elements of trial design may be influenced by their hope of enrolling their own child in a trial.

Table 3. Engaging with patient communities in early-phase pediatric gene therapy (GT) trials.

Principle	Implementation	Illustrative example(s)
Clearly defined engagement goals and plan	Determine appropriate degree of engagement at each trial stage (e.g., design, conduct, dissemination) [57, 61–64]	• Determine degree of engagement (ranging from question-specific consultation to full partnership [71]) • Clearly communicate desired patient community input at each trial stage, or collaboratively determine types of useful input at each stage
Inclusivity	Aim for representativeness and diversity of engaged patients/families [62–64]	• Engage patients/families with a range of perspectives (including patients/families not in an organized group) [72] • Use purposive rather than convenience sampling to increase representativeness [72] • Consider strategies for eliciting children's perspectives in pediatric trials [67] • Avoid tokenism [57, 58]
	Reduce barriers to engagement [62–64]	• Make reasonable time requests • Provide accommodations (e.g., for disability or different languages) • Compensate engaged patients/families when possible
Co-learning	Provide necessary training for engaged patients/families and researchers [57, 61–64]	• Educate patients/families on language and process of research to enable them to participate effectively • Educate researchers on patient engagement principles and practices
Clear communication and transparency	Communicate clearly and regularly [58, 61–64]	• Be consistent in communication with patient community (possibly designate one contact person) • Use understandable language • Establish a consistent and accessible platform (e.g., website, social media) for communication
	Be transparent [58, 62, 63]	• Identify and manage conflicts of interest (e.g., financial stake in trial, enrolled child in trial) among researchers and engaged patient community members • Clearly communicate key trial decisions and rationales (if this does not impinge on other obligations, such as protecting participants' privacy or competitive interests)
Constructive interaction process and style	Cultivate mutual respect and participatory culture [61–64]	• Respect patient community members' experiential expertise • Listen, respond to, and (if appropriate) act on patient community input • Acknowledge patient community's contributions to research (e.g., in published reports)
	Address conflicts promptly and explicitly [61]	• Establish process for soliciting and responding to patient community concerns • Revise decisions if necessary
Assessment and impact	Regularly assess engagement process [61, 63, 64]	• Solicit feedback (e.g., researcher and patient/family satisfaction) • Revise engagement process as necessary

Principles were synthesized from guidance for patient engagement in clinical research [57, 58, 61–64].

While there is substantial literature on general strategies for patient engagement [57, 58], there is comparatively less guidance for how to engage with a patient community that has made major investments in research [10, 59, 60]. Nonetheless, existing patient engagement frameworks share core principles that can be applied when engaging with highly invested patient communities (Table 3) [57, 58, 61–64]. For example, engaging a representative and diverse sample of patients and caregivers ("inclusivity") can ensure that decisions about trial design are not disproportionately influenced by the most vocal or well-connected community members (who may still facilitate effective communication with the community at large). In addition, disclosure is a widely recognized safeguard against conflicts of interest ("clear communication and transparency"), and can be a precursor to managing such conflicts [65]. Transparency about trial design and participant selection criteria (with protections for patients' privacy) may be particularly valuable for mitigating rumors and "trial envy" that can arise when a patient community is well-connected through social media, as can be especially true for rare disease communities [66].

Importantly, existing engagement frameworks and strategies may need to be adapted or refined to accommodate a particular patient community or trial [58]. For example, in early-phase GT trials involving more mature children, investigators might consider strategies for eliciting their perspectives in addition to their parents' or caregivers', and for navigating patient engagement when the priorities of these groups diverge [67]. Additionally, investigators and others could continue to develop, assess, and improve strategies for patient engagement—a crucial step toward respecting patient communities and meaningfully improving (rare disease) research [60, 68].

How should investigators navigate disagreements with patient communities that are engaged in a trial?. When a patient

Box 1 Points to consider for early-phase pediatric gene therapy trials

Evaluating risks and potential benefits

When is there enough preclinical evidence to begin clinical trials?

1. Investigators, IRBs, sponsors, and regulators should evaluate a trial's risk–benefit profile in a systematic and evidence-based way, accounting for uncertainty in the type, magnitude, and likelihood of benefits and harms.
2. Higher-quality preclinical studies have higher predictive value and thus reduce uncertainty.
3. Contextual factors may also influence judgments about whether trial initiation is ethically justified.

How should risks and benefits be balanced in dose selection?

1. Dose selection can involve tradeoffs between reducing risks and enhancing benefits.
2. In trials where vector immunity would prevent GT readministration, designs that enhance potential benefits for participants (e.g., higher starting dose, rapid dose escalation) may be ethically preferable.
3. Investigators might engage with the patient community, as well as other stakeholders—including the IRB, DSMB, regulators, and preclinical collaborators—when making dosing decisions.

Selecting participants fairly

Should trials target patients with earlier- or later-stage disease?

1. In GT trials for progressive diseases, choosing a study population can be challenging, as the risks and potential benefits of GT may differ depending on a participant's stage of disease.
2. In the face of complex ethical tradeoffs, dosing participants in sequence rather than in parallel can allow investigators to adjust their strategy for selecting participants as the trial context changes.

How should participants be selected in high-demand GT trials?

1. In high-demand trials, defining a clear participant selection strategy is important to avoid ad hoc and potentially biased decisions.
2. Any participant selection strategy can affect three ethical dimensions of a trial: scientific and social value, the risk–benefit profile for participants, and justice.
3. Investigators should carefully consider which ethical dimensions to prioritize given the specifics of their trials. The preferred participant selection strategy will depend on the context of the trial.

Engaging with patient communities

How should investigators engage highly invested patient communities?

1. Given limited commercial interest in developing therapeutics, rare disease communities may be especially involved in shaping GT research.
2. Investigators might consider close engagement with such communities to improve a trial.
3. Existing frameworks share core guiding principles that can be applied when engaging with highly invested patient communities.

How should investigators navigate disagreements with patient communities that are engaged in a trial?

1. Engagement principles focused on a constructive interaction process can help investigators balance competing stakeholder preferences and values.
2. Investigators are ultimately responsible for ensuring the scientific and social value of a trial, and respecting the rights and safety of its participants. Thus, they should generally make final decisions in cases of unresolvable disagreement with the patient community.

community is highly invested in a trial, disagreements between investigators and patient community members about trial design may be particularly challenging. For example, in the GAN trial, members of the patient community favored rapid enrollment to give more patients the opportunity for potential benefit. In contrast, investigators, IRB members, and RAC members favored dosing participants in sequence with pauses for safety evaluation, to reduce risks to participants and enhance the scientific and social value of the trial. Such tensions are common surrounding research on rare diseases for which treatment options are limited and scientific progress can be slow [69].

Several of the general principles for patient engagement provide a foundation for balancing competing stakeholder preferences and values. For example, soliciting input on relevant trial decisions, communicating these decisions and their rationales transparently, and establishing processes for appealing and revising these decisions where appropriate ("constructive interaction process and style") can help investigators build consensus with the patient community and make defensible decisions when people disagree [58]. Such principles are characteristic of efforts to optimize the investigator–community relationship [58] and mirror efforts to promote accountable decision-making in other areas [70].

Investigators are ultimately responsible for ensuring the scientific and social value of a trial, respecting the rights and safety of its participants, and engaging with any families whose children are affected by trial-related adverse events. As such, they should generally make final decisions in cases of unresolvable disagreement with the patient community. Nonetheless, these decisions will be more defensible—and likely more acceptable to patients and families—when the patient community has been engaged through principles such as those described above. Predefining a clear engagement plan may help investigators avoid and navigate disagreements with the patient community by prospectively clarifying any limits to the engagement process, as well as how final decisions about the trial will be made.

CONCLUSION

Many rare pediatric diseases are severely life-limiting, given a lack of effective treatments. GT holds the promise of health improvements for children with these and other diseases, yet unresolved ethical challenges surround its early-phase clinical testing. Drawing on our experience in the GAN trial, this review offers points to consider for risk–benefit evaluation, fair participant selection, and engagement with the patient community in early-phase pediatric GT trials (Box 1). We hope that our analysis, and further work in this area, can be of practical use to investigators, sponsors, IRBs, and others navigating the ethics of these trials.

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COMPETING INTERESTS

The authors declare no competing interests.

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