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REVIEW ARTICLE

Somatic Gene Therapy Research in Pediatric Populations: Ethical Issues and Guidance for Operationalizing Early Phase Trials

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Abstract

Currently, pediatric research involving investigational gene therapies (GT, used without intending to imply a therapeutic effect) targets a broad range of indications (including rare and ultra-rare diseases) that vary in severity and availability of approved disease-modifying therapies. Because of this diversity of circumstances, there is no one-size-fits-all list of ethical concerns relevant to all uses of investigational GTs in children. Here, we review the main ethical issues, specifically those surrounding the current state of knowledge about GT product-related immunogenicity, toxicity, duration, irreversibility, informed consent/assent, trial design (including the question of who 'goes first'), participant and caregiver burdens, and equity in diagnosis and access to research opportunities. Ethical issues that can be anticipated to arise in pediatric GT clinical trials, e.g., the uncertainty and risk of this research, the resultant preclusion of GT trial participants from other research, the length of follow-up monitoring, and the urgency often felt by caregivers dealing with dire, rapidly progressive conditions, should be proactively identified, addressed in accordance with existing best practices, and transparently discussed among all stakeholders.

Key Points

Gene therapy (GT) research in pediatric populations raises myriad ethical questions, some standard to all human subjects research, others unique to GT, pediatric, or rare disease research and/or research on conditions of unmet need.

We address such issues as the selection of target conditions and trial participants, the siteselection of trial locations, the financial and psychosocial impacts of trial participation on children and their caregivers, and the complexities of informedconsent/assent.

The article also provides guidance as to how best to manage the foreseeable ethical complexities that will accompany this research.

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1 Introduction

Gene therapy (GT) is an umbrella term describing a therapeutic mechanism in which genetic material is delivered to specific somatic cells, carrying instructions to change how a protein, or group of proteins, is produced in order to treat or prevent a disease in the recipient. This new genetic material is often, although not always, delivered using a viral vector [1]. Recognizing the potential of this promising therapeutic modality, biopharmaceutical industry interest in and clinical research on somatic GT products has expanded significantly in recent years. US FDA officials anticipate 10–20 GT product approvals annually by 2025, an astounding prediction given the first such approval was granted in 2017 and there have since been a total of five approvals to date [2].

Rare single-gene diseases are particularly appealing targets for GT [3]. Many of these conditions manifest in infancy or childhood, although affected children may not immediately be accurately diagnosed, resulting in them and their caregivers experiencing emotional and expensive 'diagnostic odysseys', during which symptoms may worsen and disabilities accumulate [4]. Once an accurate diagnosis is made, patients may be treated with existing therapies or, in the frequent case that none exist, referred to research or supportive care. Evidence that therapeutic efficacy of GT products may increase when delivered earlier in the course of disease magnifies the potential and urgency of GT development for

pediatric populations [5, 6]. For all of these reasons, access to GT research may be highly sought after for children with rare genetic conditions, especially those for whom there are no effective interventions [7]. Yet, GT research is still quite novel, with many unanswered questions about basic factors such as its short- and long-term safety, durability, and preferred modality of administration (*in vivo* vs. *ex vivo*, intravenous vs. via central nervous system, intravitreal, subretinal, etc.). As such, the decision to conduct GT research, especially on children who may lack the capacity to provide assent, who legally cannot provide informed consent, and for whom medical decisions are made by adult decision makers, raises myriad ethical questions.

This is not to say GT research should not be done; indeed, research on promising interventions for serious and life-threatening conditions with unmet need is essential. Nor do we claim that such research should not be done in children: pediatric research is necessary to ensure the development of safe and effective therapies for child patients. However, in order for pediatric GT research to be scientifically and societally acceptable, and to ensure buy-in of essential stakeholders such as patients, caregivers, clinicians, and regulators, it must be conceptualized and executed with acute attention to ethical concerns. Here, we enumerate some of the major ethical issues currently facing GT clinical trials in children and discuss first steps toward appropriately addressing them. In many cases, these are not novel issues but rather 'bread and butter' ethical issues that arise in clinical research. Nevertheless, common research ethics issues can become more complex when research participants are children, as well as when research is conducted in patients who have serious or life-threatening diseases for which there are not satisfactory cures or disease-modifying therapies. Additionally, rare disease trials tend to be small, leading to a sense of urgency (on the part of caregivers, if perhaps not in pediatric patients themselves) to secure spots in the study [8]. Common research ethics issues, such as the validity of informed consent/assent, can acquire additional complexity when situated at the confluence of novel interventions, research involving children, severe or life-threating conditions without adequate treatments, time-limited decision making, limited opportunities to participate in research, and hype over experimental interventions.

GT trials are underway for a wide array of genetic conditions. Some of the indications of interest are rapidly progressive and life-threatening but others are not; some of the trials concentrate on neonates, while others enroll older children or adolescents; and while there exist no acceptable alternative therapeutic interventions for many of the indications for which GTs are being developed, in some cases there are approved, viable alternatives. Thus, it would be irresponsible to make simple declarative statements along the lines of 'pediatric gene therapy trials should do X'. Rather, when evaluating the ethics of pediatric GT trials, determinations will vary in response to contextual issues, including the indication of interest and its characteristics, the target trial sample, the availability of alternative treatments, and other such factors.

2 Ethical Issues Surrounding Approaches to Gene Therapy Development and Administration

GT can be administrated to a recipient via a viral vector (*in vivo*) or it can entail the extraction of autologous material from a patient, manipulation of that material's genetic structure, and then re-insertion into that patient (*ex vivo*). Both of these approaches raise ethical issues. Key ethical concerns center around the scalability and accessibility of GT interventions. Ideally, GT will become widely available to all patients who would benefit from it; at the moment, however, there is insufficient infrastructure to scale-up *ex vivo* approaches in particular, and also *in vivo* approaches. The resource-intensiveness of these approaches mean that they are unlikely to become widely accessible in situations of limited resources, whether that be underinsured communities in the US, publicly funded health care systems such as those of Canada or the UK, or low-income nations. Thus, we foresee serious and persistent challenges to equity of access and just distribution of GT products. Serious efforts and investment will be required in order to try to make the benefits of these products widely available.

In addition, there are ethical concerns that stem from the science of GT interventions. These center largely around immunogenicity and toxicity. While not all GT approaches involve viral vectors, at present many do. There are limitations to using viral vectors, beginning with vector selection. The distribution of viruses varies geographically, thus the selection of a viral vector has implications for the feasibility of use of that GT product, as the prevalence of pre-existing antibodies to the chosen virus may vary among populations of different global regions [9].

A further complication is that after an individual has acquired neutralizing antibodies to a virus (either through natural infection or after receipt of a GT product that used that virus as a vector), a second exposure would trigger the recipient's immune systems to destroy the virus, before (in the case of GT) it is able to affect the desired genetic change. As a result, there is currently no opportunity for individuals to receive a second dose (or another GT product that uses the same viral vector), even if the effects of the GT wane over time or if there was no effect from the initially administered product. Even when there is an effect, the duration of this is currently unknown and may vary depending on such factors as the volume of GT product initially delivered, the

cell type(s) to which it was delivered, or the age and stage of development of the GT recipient [10]. For these reasons, continued research into such issues as re-dosing, durability of effect, and variability between cell types is a moral imperative for stakeholders engaged in GT research.

Regardless of whether *ex vivo* or *in vivo* approaches are pursued, safety concerns exist for all GT research. Unlike the ongoing administration of small molecule drugs, if a toxicity is noted in a patient, the GT cannot yet be 'turned off'; once administered, it will be present in the patient for an unknown period of time, potentially of long duration. Furthermore, participation in a GT trial often precludes enrollment in other clinical trials, including those with non-GT agents. This is a concern, especially for early phase trials where there is little to no prior use of the GT product in humans and where there may well be no benefit to participants. Furthermore, there is no guarantee that a GT product will only affect the intended tissue, raising concern about potential off-target effects, such as the activation of cellular oncogenes by insertional mutagenesis [10–12]. There is also no guarantee that the volume of GT product given will be correct, neither too low nor too high. As such, GT research should only occur when there is reason to believe (for example, on the basis of research in animals) that the intervention is more likely to result in benefit than harm to participants. Indeed, the FDA, pursuant to 21 Code of Federal Regulations 50, subpart D, requires that pediatric research must offer participants a prospect of direct benefit sufficient to justify the risks of the research (although claiming that early phase trials offer the prospect of direct benefit may be an overstatement and may increase the likelihood of therapeutic misconception, in which research is construed as clinical care) [13, 14].

First-in-human and early phase studies always entail uncertainty and a heightened possibility of risk. In the case of GT, this risk and uncertainty are further heightened given the relative newness of the GT approach, its current irreversibility and unknown duration, the fact that some conditions for which these products are being tested have no animal models that directly emulate the human disease, the lack of known natural history data for many rare conditions, and pressure from caregivers and patient advocacy groups to advance the research quickly, particularly in the case of rapidly progressive conditions.

3 Informed Consent/Assent

Human subjects research raises issues of informed consent and research on children raises issues of assent. All research, and especially early phase research, poses unknowns that must be conveyed to potential participants or their surrogate decision makers, and all research in patients raises the specter of therapeutic misconception (in which participants mistake research for clinical care) or therapeutic misestimation (in which participants overestimate the likelihood of benefit from participation) [15, 16]. GT trials in children face these common research ethics issues; further challenges to informed decision making are posed by the previously described unknowns inherent to GT research. Elements of traditional informed consent include provision of information such as the nature of the medical condition and proposed alternative treatment options along with their likelihoods of success, as well as assessment of the patient's (and where applicable) surrogate decision maker's understanding and voluntary agreement. With children and adolescents, in addition to supplying ample time for decision making and responding to questions they may have, it is imperative that developmentally appropriate language and engagement is incorporated into the consent process [17]. In addition to a guardian's legally binding permission for the child to participate in the research study, pediatric assent, including active solicitation of the patient's willingness to accept the proposed intervention, must be obtained for children and adolescents with the cognitive and decisional capacity to provide their input. The 'Mature Minor Doctrine' found in the US and Canada, stipulates that an unemancipated minor patient may possess the maturity to choose or reject a particular health care treatment, sometimes without the knowledge or agreement of parents, and should be permitted to do so [18]. Our current understanding of ideal medical decision making is that it be shared, involving children, family members, and health care providers. GT, like other types of novel, early phase research, raises additional barriers to that shared decision making because of the high degree of uncertainty about the safety, efficacy, and durability of GT, often accompanied by a lack of alternative treatment options and/or urgency of treatment [19].

Uncertainty surrounding experimental interventions complicates the disclosure of risks and benefits required for informed consent and assent. While FDA regulations mandate that children participating in research posing greater than minimal risk, which describes all GT clinical trials, have the prospect of direct benefit from the research, it is impossible in the early stages of GT research to calculate the likelihood of benefit. At the same time, it is clear that administering a GT via a viral vector will result in that individual being precluded from receiving other GT products that use that vector. After a patient participates in a GT trial, they will be unable to participate in other such trials or to use an approved GT product that uses the viral vector to which they were exposed until re-dosing is achievable. The individual will also likely be excluded from non-GT research.

Research participants are informed of the expected duration of participation and of their ability to withdraw at any time; however, these considerations lose much of their meaning when exposure to a GT agent cannot be undone

or effects 'turned off'. This characteristic of GT has implications for research participants, including the potential development (quickly or over time) of unknown serious adverse events, such as may occur from a GT product having off-target effects or being delivered at a non-optimal dose [20]. Furthermore, a person's willingness to participate in research may change over time, especially if the research is construed as burdensome. This fact is particularly relevant to GT research, given the FDA's call for long-term follow-up for a minimum of 5 and more commonly 15 years [21]. While recipients of investigational GT products currently have no way to halt the effects of the intervention, they may nevertheless decide to quit a trial, which means they would stop being monitored and contributing to ongoing data collection. Thus, for GT research conducted on children, there is a dual mandate that if a former child-turned-adult participant decides to leave the trial, this must be respected. At the same time, it must be emphasized to all participants how crucially important their participation is to obtaining long-term safety and efficacy knowledge for the benefit of an entire population of patients [22]. Long-term follow-up poses serious operational challenges; for example, what happens if a sponsor goes out of business or is acquired by another company? There is an urgent need for community discussion about what is needed to make long-term follow-up a reality and which entities have what responsibilities to ensure these data are responsibly collected and shared in order to advance our understanding of the effects of GT products over the long-term.

4 Who Goes First and Other Questions of Trial Design?

There are numerous questions facing sponsors of GT clinical trials, including the following: which viruses are being chosen for use in this research and which populations might those choices advantage/disadvantage? What should sponsors do for their former trial participants once re-dosing is practicable or while re-dosing research is underway? Which patients are recruited for GT trials and why? We address this last point here.

Evidence that GT may be more effective when delivered earlier in disease progression magnifies the potential of GT for pediatric populations battling devastating conditions [5]. When a child has a rapidly progressive and/or ultimately fatal condition, it is less likely for their families/caregivers to object to enrolling them in GT trials, even though the child is perhaps unable to provide meaningful assent (or any assent at all, as in the case of trials involving neonates or fetuses). Whether or not the child benefits from the trial, they will be precluded from future use of GT products using the same virus and likely from all sorts of interventional research. Preclusion from future research should be a significant factor in the decision-making calculus for potential trial participants (and/or their surrogate decision makers) [6]. However, this consideration may be of less concern in rapidly progressive conditions (in which the focus is on the immediate rather than longer-term future) than for conditions that are slower to progress. In the latter situation, the risk/benefit ratio of participating in a GT trial may flip from the notion that the GT offers an opportunity for benefit that can be ethically pursued to the notion that it would likely be better to wait to try a more developed GT product rather than risk an earlier, less proven one. Individuals, of course, vary in their risk tolerance and thus in their decisions about whether to try an unproven intervention. It might be that a patient with a slowly progressing disease may still choose to try an unproven GT intervention; however, such a choice would require assurance that this was an informed, voluntary decision made with knowledge of the resultant trade-offs and opportunity costs [23, 24].

When designing trials, the question of who to include in the initial trial sample is a weighty one that should be discussed proactively with the patient community [25, 26]. In addition, there are questions about where these trials should be sited, an issue impacted by numerous structural, operational, and strategic considerations. Ethical considerations must be added to the factors to be considered. Trials for rare indications typically enroll a smaller number of patients than do other types of clinical research and are likely to have only one or very few trial sites, both of which factors increase the difficulty of enrolling and participating in a trial. This, in turn, has implications for equity of access to research opportunities. Furthermore, ongoing challenges with manufacturing capacity limits the quantity of GT products available for use in clinical trials and via non-trial preapproval access ('compassionate use') [27, 28]. Stakeholders should thus consider equity of access and opportunity for all relevant patients when establishing the number and location of trial sites.

Even decisions about which diseases are targeted for drug development efforts raise justice concerns. Concentrating development efforts on single-gene mutations is currently seen as a practical and efficient approach, and decisions regarding GT targets are impacted by factors such as limitations to the size of transgenes that vectors can carry [28]. Nevertheless, there remain thousands of serious genetic conditions with high unmet need. Biopharmaceutical, patient advocacy, and legislative stakeholders must constantly track which indications are the subject of development programs (and which are not) to prevent the neglect of those conditions that appear amenable to GT intervention but offer limited financial reward (due to having small patient populations or being disproportionately present in less wealthy regions) or do not have established, vocal advocacy efforts to

press for attention. It is not sufficient for well-organized and well-resourced rare disease communities to receive the bulk of research and industry attention; justice requires efforts to help underserved communities successfully advocate to be the subjects of GT research, if they so choose.

5 Trial-Related Participant and Caregiver Burden

5.1 Financial and Opportunity Costs

Clinical trial participation of all types entails costs, both financial and non-financial. Pediatric trials may be particularly costly in that patients must be accompanied on trial-related visits by adult caregivers who may have to balance the demands of the research with other obligations, such as employment, elder care, or the care of other children. Participation in GT research may entail having to spend considerable time at the trial site (for screening, pre-dosing preparations that may involve intensive conditioning regimens, and post-dosing observation), exacerbating the demand on participants and caregivers. The small size of GT trials and their limited number of sites may well result in participants (and would-be participants who come to be screened) hailing from distant locations. As such, they may need to temporarily relocate (including across national borders), increasing both demands on the adult caregiver and financial costs. This is especially taxing if the patient and caregiver are burdened by the expenses that accompany living with a rare disease [24].

All sponsors, especially those who are conducting GT research on pediatric patients, should be cognizant of the financial and opportunity costs these trials pose for participants and their caregivers. Sponsors should seek to mitigate the impact that these burdens have on equity of access to trials by reimbursing for related travel, accommodation, and childcare expenses, and providing assistance with securing satisfactory housing and transportation. As noted previously, sponsors should also consider equity of access and opportunity when establishing trial site locations and when choosing single- versus multi-site trial designs—decisions that are limited by scalability challenges to vector and transgene production as well as the lack of a consistently robust referral network to steer patients to research opportunities [28]. Growth of such necessary 'infrastructure' as manufacturing capacity, work forces, and institutions capable of conducting high-quality GT research will, over time, help ease demands on trial participants and their caregivers by relieving current capacity bottlenecks. However, at present, protocols should be designed with an eye toward limiting participant visits to trial sites and instead considering the integration of remote and virtual options to the extent this can be safely done. For example, sponsors might permit routine laboratory work to be performed at a medical center near the participant's home, utilize visiting nurse services that travel to the participant's home, or conduct some assessments via telemedicine options [29, 34].

5.2 One Family, Multiple Patients

As genetic conditions may run in families, it may be that more than one individual in a family is impacted. The need to care for multiple patients may exacerbate the burdens of trial participation. Furthermore, situations may arise in which similarly affected relatives are differentially eligible to participate in a trial, resulting in potential tensions if one is able to participate in a study while another is not [27]. In addition to the psychosocial stresses that may arise from this situation, there is also the fact that a GT trial participant, once exposed, will shed the viral vector [30]. This poses the risk that patients outside of the trial may also be exposed to the virus, either through direct contact with the trial participant or indirectly through others who had contact with the participant, potentially leading them to develop neutralizing antibodies to the virus and thus foreclosing their future opportunity to try GT products that use that viral vector. In order to prevent such a possibility, close contacts (such as siblings) who have a shared condition but who are differentially eligible for GT trials should be separated for an unknown period of time to prevent transmitting the virus to the individual who is not in the trial, unless provisions are made to provide the investigational GT product to the non-trial-eligible patient through Expanded Access or some other mechanism [27]. Separating close contacts for a period of time will increase the financial and practical burden on caregivers and perhaps also create psychosocial distress, especially if children are unable to understand the reason for the temporary separation. In this case especially, and also in general, sponsors and clinical trial sites should be proactive in thinking about how to ameliorate financial and psychosocial stress of trial participants, their caregivers, and other immediate family members, including through the provision of counseling services. There is also an urgent need to better understand the ways by which viral vectors are shed and for how long.

5.3 Long-Term Follow-Up

Given the FDA's call for long-term follow-up, the burdens of trial participation will continue after administration with the investigational GT product. Depending on what the follow-up entails, some of this could be done remotely, as suggested previously. Research follow-up should, as much as possible, be timed to occur in tandem with clinical care, so as to minimize participant and caregiver burden. As mentioned

previously, there is an urgent need to develop procedures and infrastructure to make long-term follow-up a feasible reality. These data need to be collected and shared in order to advance our understanding of the effects of GT products over the long-term; however, we cannot meaningfully require this unless so doing is feasible, which may entail resources beyond that of individual sponsors.

6 Ancillary obligations

6.1 Genetic Testing, Diagnosis, and Appropriate Clinical Care

As sponsors and other stakeholders seek to address equity and accessibility issues for GT research, they must also address the related issues of inequitable access to genetic testing, diagnosis, and clinical care, within the US and globally. A caregiver cannot begin to consider enrolling a child into a GT clinical trial until they have a diagnosis and know of any existing therapeutic and research options. This requires a system in which children are both accurately diagnosed and routed to appropriate care providers; yet, as mentioned previously, many rare disease patients and their caregivers experience costly and frustrating diagnostic odysseys. While it is not the role of GT sponsors to overhaul access to genetic diagnosis and care, they would benefit from doing so, both in terms of enlarged pools of potential trial participants and of potential customers for GT products brought to market. As an example, Novartis, the manufacturer of Zolgensma, an FDA-approved GT treatment for spinal muscular atrophy, has worked to promote newborn screening efforts that would identify spinal muscular atrophy at birth [31]. Sponsors and other stakeholders also have a role to play in educating the general public and clinicians about rare diseases. Many children with rare diseases receive services from an array of health care providers (such as pediatricians, specialists, therapists, dietitians, etc.), all of whom need to understand what investigational and approved GT options exist for their patients, as well as the anticipated effects and risks of these interventions [32].

6.2 Data Sharing

In order to get the most promising GT products to the patients who would benefit from them in the most rapid and safest possible way, companies, investigators, and regulators should share information. Sharing both accelerates understanding of the relevant risks and benefits of various GT approaches (which has follow-on implications for both informed consent and the calculation of benefit/risk ratios) and prevents the conduct of similar or identical research for the sole reason that those involved were unaware of others' efforts. Implementing and prioritizing data sharing will be to the benefit of, most importantly, patients and caregivers, and also companies, regulators, and clinicians, by limiting repetition of ineffective or harmful approaches and spreading knowledge of successful approaches. Data sharing is particularly urgent when it comes to serious adverse events, as reporting of these may prevent future harm to trial participants and/or patients.

7 Conclusion

For years, the benefit of GT was only a promise. Today, with five GTs having been approved by the FDA and many more in clinical development, that promise has begun to materialize, to the delight of patients and caregivers, clinicians, and the individuals and companies that reap the financial and reputational rewards from these successful products. Yet, just as the untimely death of GT research participant Jesse Gelsinger in 1999 put the brakes on the entire field of GT for years, unanticipated negative outcomes could once again squelch what is currently a dramatically increasing area of investment, activity, and aspiration. Such negative occurrences may be deaths or injuries of research participants, and they could also be situations that cast an unfavorable light on GT, for example, by calling into question the robustness of informed consent on the part of participants or their surrogate decision makers. As such, it is essential to proactively scrutinize the GT research enterprise, both to identify areas of concern and to note and disseminate best practices. Accordingly, in this paper we have scrutinized pediatric GT research in light of the myriad ethical challenges that currently exist or are foreseeable, and, where possible, provided guidance for managing these complexities.

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