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# Siblings and Discordant Eligibility for Gene Therapy Research: Considering Parental Requests for Non-Trial "Compassionate Use"

Clinical Ethics

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## Abstract

Deciding whether to grant an expanded access request for a child whose sibling is enrolled in a gene therapy trial involves a number of complex factors: considering the best interests of the child, the psychosocial and economic impact on the family, and the concerns and obligations of researchers. Despite the challenges in coming to a substantively fair outcome in cases of discordant eligibility, creating a procedurally fair decision-making process to adjudicate requests is essential.

## Keywords

Bioethics and medical ethics, pediatrics, biomedical research, justice, gene therapy, expanded access

## Case

Peter, aged 6, and James, 3, both have Duchenne muscular dystrophy (DMD), a life-limiting genetic disorder. James and Peter's mother, Susan, who is active in the US Duchenne community, learns about a Phase 2 clinical trial studying an experimental DMD gene therapy. Susan enquires about enrolling her sons as trial participants. The researchers inform her that Peter is within the trial's age range of eligibility, but James is too young. Peter undergoes screening, is found to be eligible and willing to participate, and, after Susan provides parental permission, is accepted into the trial. Although participation in this trial will likely rule Peter out from any future trials, gene therapy or otherwise, Susan decides to enroll him. Susan then requests access to the investigational gene therapy for James via expanded access (EA). EA is a regulatory pathway by which patients in the United States with life-threatening or serious diseases or conditions for which no satisfactory approved therapy options are available and clinical trial participation is not possible can use experimental medical products outside of a clinical trial, provided the biopharmaceutical company developing the drug agrees to provide it and conditional on Food and Drug Administration (FDA) and institutional review board (IRB) approval. The company developing the gene therapy has not established how it will consider requests stemming from

siblings who are discordantly eligible to participate in its trial.

## Context

DMD is characterized by progressive muscular degeneration caused by alterations to the dystrophin protein, which is needed to maintain the integrity of strained muscle.<sup>1</sup> It primarily affects boys. Most boys with DMD present between the ages of 3 and 5; as such, it is not uncommon for parents to have more than one child before realizing the elder has a life-limiting genetic condition.<sup>2</sup> Duchenne is an X-linked condition. Although 30% of cases are caused by spontaneous mutations,<sup>3</sup> it is usually passed from women who are carriers of the genetic mutation. If a woman carries a mutation in the gene that

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encodes for her dystrophin, there is a 50% chance she will pass on this gene to a child.<sup>4</sup>

DMD experimental gene therapies often use a viral vector to introduce a working version of a gene that codes for the production of dystrophin into a patient's cells.<sup>5</sup> While clinical trials are in progress, there is currently no FDA approved gene therapy for Duchenne.

### The interests of the ineligible child

Peter and James will experience progressive muscle weakness, resulting in eventual loss of ambulation, impaired pulmonary and cardiac function, and then acute cardiac and respiratory failure, leading to early death.<sup>2</sup> The only treatments available are non-curative, which can (in some subgroups of patients) delay progression rather than prevent it, or improve quality of life and lifespan, for example non-invasive ventilation.<sup>6</sup> However, there are risks inherent to experimental gene therapies that may be considered untenable by a parent, even considering this prognosis. Because gene therapies are so new, their safety, effectiveness and durability is not fully known.<sup>7</sup> There have been several deaths among gene therapy trial participants that appeared to have directly resulted from the experimental intervention.<sup>8,9</sup> Other gene therapy recipients have suffered serious or life-threatening adverse events.<sup>10</sup> Thus far, two experimental gene therapies being tested for use against muscular dystrophy have resulted in serious adverse events.<sup>11–13</sup>

Also, because optimal dosing has not yet been established, there is no guarantee that James will receive a high enough dose to provide him therapeutic benefit, even if the intervention is found safe and effective. The viral vector used to deliver the product will result in recipients developing an immune response to that virus that would preclude redosing at any level.<sup>14</sup> Thus, even if this investigational product fails, he will not get to try it, or any other gene therapy that uses the same virus, again. Even if James would assent to EA at this time if offered it, his autonomy may not be best respected by limiting his future options in the pursuit of uncertain clinical benefit.

Age is relevant: if possible, it may be better for James to wait to participate in a later-stage gene therapy clinical trial – when more is known about dosing, safety, and efficacy – or to wait until a gene therapy is approved by the FDA. Furthermore, James' ability to understand what is being proposed will increase during the process of waiting as he matures. However, the benefits of waiting must be weighed against the fact that the longer a child goes without adequate dystrophin, the more irreversible damage accumulates. By waiting, there is also a risk of James encountering the virus used to deliver the gene therapy through

environmental exposure and becoming ineligible to use any product delivered via that virus.

### Psychosocial and economic issues for family and caregivers

The atmosphere of hope and expectation that surround gene therapy trials<sup>15–17</sup> may increase the predisposition of families to have their children enrolled in these trials or to find non-trial avenues to receive the gene therapy if they are ineligible. Participation in a clinical trial almost invariably places significant social and economic burdens on families, and enrolling can mean significant opportunity costs. Gene therapy trials, which can entail several long stays at trial sites, may require relocating all or part of a family to a new location, with the stress and logistical challenges this entails. Non-trial access would involve at least some of these opportunity costs, as the intervention must be given in a controlled and monitored manner.

In this case, these challenges are heightened. Both boys are too young to meaningfully make their own treatment decisions, though efforts should be made to help them understand their options to the extent possible. After receiving the experimental intervention, Peter would likely shed the viral vector for an indeterminate amount of time. As such, he could infect James, who might then develop an immunity to the vector, rendering him incapable of using any interventions administered by this vector. Prudent caution for James would therefore include isolation from Peter for an unknown period of time, in order to best ensure James' future ability to receive a gene therapy. Such separation need not happen if both boys were to receive the gene therapy at the same time, Peter through the trial and James through EA. However, 'at the same time' may be hard to achieve, particularly given the fact that the volume of gene therapy product being produced is quite modest and trials are designed to accommodate only small numbers of participants. If only Peter received the intervention at this time, it would be extremely challenging to separate the boys, particularly if Susan is their sole caregiver. Even if James and Peter have another caregiver, non-simultaneous administration would entail separation of the family. In either case, severe financial and psychosocial burdens may be incurred, especially if the young children do not understand why the family must be separated. Trial sponsors often provide financial support of costs directly associated with the trial to participants' families, but it is unclear if a sponsor would be willing to do likewise for a child receiving the experimental product outside of a research clinical trial.

Additionally, if the EA request for James is refused, there is the possibility that Susan and/or Peter will feel guilt for Peter receiving a potentially life-altering intervention at a time when it is unavailable to James. As James matures, he may feel envy or resentment for not having had the same opportunity as his brother. Alternatively, if Peter does not benefit from the trial and James is later able to receive an improved version, their relationship may have aspects of jealousy and/or survivor's guilt. If James develops immunity to the virus used as a vector in Peter's trial, there may be a sense of guilt on Peter or Susan's part, even though James' viral exposure may not have been trial-related. Also, James' age and early stage of development means that his separation from Susan, as she accompanies Peter through the trial, comes with the risk of affecting his caregiver attachment, stress levels, and potentially even brain structure.<sup>18</sup>

Alternatively, if James received the intervention through EA, the family may experience feelings of resentment from others in the DMD community. Given the fact that there is far more interest in receiving gene therapies than there are available enrollment opportunities in trials, how might the relationship between Susan and other parents change if James receives the intervention through EA because his brother was enrolled in the trial, while other children are unable to obtain it? Unless the intervention is available on an equitable basis via EA for all who desire it, are physically eligible to receive it (e.g., not immune), and are unable to participate in the trial, it seems likely that there will be some perceptions of unfairness, particularly in a closely-knit rare disease community where it is unlikely that Susan would be able to conceal news of James' treatment via EA. Yet large scale EA for gene therapy – enough to provide the experimental intervention to all who desire it - is unlikely.<sup>19</sup>

### Concerns for researchers

Gene therapy production is currently extremely expensive and entails a complex manufacturing process. There would be severe logistical challenges in increasing production sufficiently to develop product above that necessary for a clinical trial.<sup>19</sup> Indeed, such additional production may be simply impossible, given demand currently outweighs the capacity of gene therapy manufacturers.

EA, by law, may be offered only to patients ineligible for clinical trial participation and therefore should not undermine trial enrollment.<sup>20</sup> However, offering EA may reduce an already limited number of consumers for approved future treatments for such rare genetic diseases, particularly in light of ongoing immunogenicity concerns that would render the recipient of an intervention unable to try others that use the same viral

vector. This provides a financial disincentive for the company to offer EA. Moreover, companies may fear that side effects in an EA recipient will result in negative publicity, potentially leading investors to back away and to place their current and future trials in jeopardy with regard to enrollment.

Nevertheless, sponsors have responsibilities in the case of siblings with the same condition who are discordantly eligible to participate in a gene therapy trial. First, they must practice epistemic humility in conveying to families the extent of the uncertainty surrounding gene therapy, on issues like risk, redosing, and immune response. Moreover, researchers must provide counseling support to families, as is often offered with other serious medical procedures such as organ donation.<sup>21</sup> Families could also be placed in touch with (willing) previous trial participants, who may be able to offer emotional support and advice.

Finally, in 2010, the Committee on Drugs and Committee on Pediatric Research described the potential risks involved in pediatric studies as including: “separation from parents, family, or friends; effects on growth and development.”<sup>22</sup> By enrolling Peter in a trial, the researchers are also imposing these risks on James, as well as the risk of viral exposure and its consequences. Since the Common Rule, which governs human subjects research conducted under the auspices of certain US agencies but is frequently voluntarily applied to all human subjects research regardless of funding source, demands that greater than minimal risk research in children carry some potential for direct benefit,<sup>23</sup> it could be argued the sponsor is obligated to provide possible benefit to James. This benefit could plausibly be access to the intervention via EA.

### Conclusion: Procedural and substantive fairness

Although it is hard to say what would be a substantively fair outcome in sibling cases, it is comparatively easier to create a procedurally fair decision-making process to adjudicate EA requests. Procedural and substantive fairness are distinct ideas. Consider the difference between a lottery and a criminal trial. A lottery is procedurally fair if everyone is able to enter, everyone knows how the lots are drawn, and the draw is done transparently so all can witness that the process has not been perverted. That says nothing, however, as to whether drawing lots is a substantively fair procedure by which to allocate a good. By contrast, the procedural elements of a trial, for example the right to a defense, are designed to generate certain substantively fair outcomes: the determination of guilt and the acquittal of the innocent.



A number of the psychosocial issues raised in this paper may be mitigated if research sponsors produce clear, publicly available policies concerning how and by which criteria sibling requests would be considered: a transparent, procedurally fair process that researchers and families are aware of before cases become a reality. At this time, it is believed that only one company (PTC Therapeutics) has created such a policy for an investigational product, and it was not in the context of a gene therapy trial.<sup>24</sup>

This is not to say that concerns of substantive fairness – for example, whether it is fair for a sibling to get EA but not an unrelated child, particularly if the latter might be anticipated to derive more clinical benefit from the intervention – are unimportant. But the factors that go into such judgments are complex and deeply contextual. Provided processes are designed with engagement from all stakeholders, and critically engage with the ethical issues raised in this commentary, then the procedurally fair policy that results from this deliberation could guide researchers in responding to Susan's request for EA access for James. The response may be refusal or acceptance, but it needs to be arrived at by a procedurally fair process.

If the decision is to make the investigational product available outside of a clinical trial for the trial-ineligible sibling, those involved must then assume responsibility for performing the procedure in an ethical manner, including securing pediatric assent (as possible) and parental permission, and ensuring it is carried out in accordance with all relevant oversight bodies, including the FDA and the IRB.

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