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Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy

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Background The social context of rare disease research is changing, with increased community engagement around drug development and clinical trials. This engagement may benefit patients and families but may also lead to heightened trial expectations and therapeutic misconception. Clinical investigators are also susceptible to harboring high expectations. Little is known about parental motivations and expectations for clinical trials for rare pediatric disorders.

Purpose We describe the experience of parents and clinical investigators involved in a phase II clinical trial for Duchenne and Becker muscular dystrophy: their expectations, hopes, motivations, and reactions to the termination of the trial.

Methods This qualitative study was based on interviews with clinical investigators and parents of sons with Duchenne and Becker muscular dystrophy (DBMD) who participated in the phase IIa or IIb ataluren clinical trial in the United States. Interviews were transcribed and coded for thematic analysis.

Results Participants were 12 parents of affected boys receiving active drug and 9 clinical investigators. High trial expectations of direct benefit were reported by parents and many clinicians. Investigators described monitoring and managing parents' expectations; several worried about their own involvement in increasing parents' expectations. Most parents were able to differentiate their expectations from their optimistic hopes for a cure. Parents' expectations arose from other parents, advocacy organizations, and the sponsor. All parents reported some degree of clinical benefit to their children. Secondary benefits were hopefulness and powerful feelings associated with active efforts to affect the disease course. Parents and clinical investigators reported strong, close relationships that were mutually important. Parents and clinicians felt valued by the sponsor for the majority of the trial. When the trial abruptly stopped, they described loss of engagement, distress, and feeling unprepared for the possibility of trial termination.

Limitations This was a retrospective study of one clinical trial. We were unable to recruit participants whose children received placebo. The interviews occurred during a time of significant uncertainty and distress for many of the participants.

Conclusion This pilot study reflects complex outcomes of strong community engagement. The findings highlight a need for renewed education about, and support for, clinical trial termination and loss of drug access. The primary positive outcome was demonstration of strong relationships among committed parents and study teams. These relationships were highly valued by both parties and may suggest an ideal intervention opportunity for efforts to improve psychological

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well-being. A negative outcome attributed, in part, to community engagement was inappropriately high trial expectations. More optimistically, high expectations were attributed, in part, to the importance of hope and powerful feelings associated with active efforts to affect the disease course. *Clinical Trials* 2013; 0: 1–9. <http://ctj.sagepub.com>

Background

Advances in research are leading to promising potential therapeutics for the treatment of rare disorders. Simultaneously, the social context of rare disease research is changing, with increased community engagement around drug development and clinical trials. Greater knowledge and personal involvement for patients and families may come with significant feelings of hopefulness and responsibility, and with enhanced assumptions about access and involvement in the clinical trial process. Greater involvement may also encourage unrealistic expectations of the patient/family role in trial execution and of the treatment under trial. Family well-being may be threatened when expectations are unrealistic and when boundaries are unclear.

Values, motivations, and relationships among clinical trial partners

Clinical trial participants

Commonly cited reasons for participating in clinical trials are altruism (e.g., contributing to science and/or helping others with the disorder) and the potential for personal benefit [1,2]. Recent studies suggest that the potential for personal benefit is at least as common, if not more common, a motivator as altruism [2–4]. Personal benefit as a motivator may reflect inappropriately high expectations for a successful trial outcome.

Bioethics scholars and clinical investigators have raised concerns about informed decision making by individuals with life-threatening disease and limited treatment options [5,6]. One particular concern is therapeutic misconception:

... when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial. [7]

Others have highlighted the importance of optimism and hope to clinical trial participants which may not stem from ignorance or confusion, that is, may not reflect therapeutic misconception [8–10];

yet unwarranted situational optimism continues to raise concerns about vulnerability to exploitation of research participants and concerns about uninformed decision making [10]. The concept of therapeutic ‘misestimation’ (an over- or underestimation of benefit or risk in a clinical trial) has been proposed as a further distinction to account for unwarranted optimism without therapeutic misconception [9].

Parent decision makers in pediatric trials

The majority of data on motivations and perceptions of trial participation come from adults making decisions about their own participation. A recent synthesis of 22 qualitative studies of pediatric oncology clinical trials [11] concluded that informed consent is difficult to achieve due to the complexity of the protocols, parents’ emotional distress, and their feelings of dependency on the child’s physician. Parents frequently and inaccurately attributed therapeutic intent to research procedures in these studies. Parents reveal desires to act in best interest of the child and fear of making the ‘wrong decision’ about their child’s participation in a clinical trial [11].

The clinician investigator

Several studies have identified role ambiguity among healthcare providers engaged in clinical research, which arises from a struggle to balance the responsibilities associated with being a clinician and a researcher [12–14], and may lead to conflicts of interest and therapeutic misconception and may undermine the authenticity of the consent process. Unwarranted optimism/therapeutic misconception has been identified among clinical investigators executing trials [7,15].

Purpose

We sought to explore the dynamic nature of stakeholder relationships in a clinical trial sponsored by a small biotech company for Duchenne and Becker muscular dystrophy (DBMD). Duchenne muscular

dystrophy (DMD) is a progressive, ultimately fatal neurological disorder with a strong advocacy and support community. Becker muscular dystrophy (BMD) is a less severe disease manifestation that is caused by mutations in the same *dystrophin* gene.

A study of 19 participants and their parents in a European trial provided data on the impact of participating in an exon-skipping trial for DBMD [16]. The impact was rated as positive (42%) or neutral (35%) by the majority of parents, and all participating families were determined to have adequate knowledge and realistic expectations of the clinical trial [16].

The ataluren clinical trial

In 2005, PTC Therapeutics reported a successful phase I trial with PTC 124 (ataluren), a compound designed to promote ribosomal read-through of premature stop codons in messenger RNA (mRNA) [17]. Early in 2006, PTC Therapeutics initiated a 28-day phase IIa clinical trial in 38 participants, and in 2008 initiated a 48-week phase IIb international randomized study with placebo, low dose, and high dose arms. Participants were 5 years of age or older and had the ability to walk ≥ 75 m unassisted, among other inclusion criteria. There were 15 US study sites. In 2009, enrollment closed after 174 patients were recruited.

In March 2010, the sponsor reported that preliminary results showed no statistically significant improvement to the primary endpoint, the 6-min walk test, for participants on the high dose. All trials of ataluren in DBMD were stopped and the investigators unblinded the study. In April 2010, detailed data analysis was presented, suggesting that low-dose ataluren may have clinical benefit [17].

At the time of the interviews for this study, the dosing of trial participants was unblinded. Parents of participants had been informed of the data suggesting benefit of low-dose ataluren. When we started interviews, boys in the trial had lost access to the drug and future access was unknown. Midway through the interview study, an open-label study was initiated for trial participants. Although our initial aim was to explore the experience of parents and clinician investigators involved in a clinical trial for a rare disorder, we were also able to explore participation in a trial that came to an abrupt, unexpected end. To date, an open-label trial (<http://www.clinicaltrials.gov/ct2/show/NCT01247207?term=ataluren&rank=9>) continues for participants in the phase IIa and IIb trials.

Study aims

This study aimed to describe the experience of parents and clinical investigators who were involved in

a phase II clinical trial of ataluren for DBMD. Specifically, we describe expectations, hopes, and motivations of each group, as well as reactions to the termination of the trial.

Methods

We conducted semistructured telephone interviews with clinical investigators and parents of sons with DBMD who participated in the phase IIa or IIb ataluren clinical trial in the United States. The topics explored during the interviews – experiences in the trial, hopes, and expectations; perceptions of benefit; and relationships among stakeholders – were informed by the literature and clinical and anecdotal experience. Because these sources suggested that expectations and hopes for a clinical trial may differ, we asked participants to describe both their hopes and expectations.

Using NVivo 8 QSR, a qualitative analysis software package, the responses were analyzed by two independent investigators (T.F. and E.B.) to ensure coding consistency and high intercoder reliability. Discrepancies in the coding were discussed until reconciliation was achieved. All analyses were based on consensus codes. We conducted thematic analysis within and between the parent group and the clinician investigator group. Major themes that arose from the analysis and illustrative quotes are presented.

Parent participants were recruited through advocacy organizations and snowball recruiting. Clinical investigators at the 15 US clinical trial sites were directly contacted. Nine investigators and 12 parents of individuals in the ataluren trial were interviewed between October 2010 and June 2011. We continued recruitment of the investigators until we achieved the highest possible participation after making three requests of each study site. We continued recruitment of parents until we achieved saturation (i.e., information redundancy). The sons of all parent participants received active drug (low or high dose) during the trial. We made a second attempt to recruit parents whose children were on placebo, but we were unsuccessful. This is described later as a limitation of this study.

Results

Participants

The study included 6 fathers and 6 mothers of 11 boys with DMD (including 1 mother–father pair) and 9 clinical investigators. All participated at US study sites.

Expectations and hopes for the clinical trial

Parents

As previously described, we asked participants to differentiate between expectations and hopes. Although participants' default terminology was 'hope', most parents were able to clearly differentiate between expectations and hopes. Participants described expectations in terms of 'what I thought would happen' or 'feeling confident about' versus their hopes as an optimistic view toward the best possible outcome.

Most of the parents reported and demonstrated being well informed about the trial. They reported multiple sources of information that contributed to the formulation of their expectations: their own research into the drug; information from advocacy organizations and parent communities; communication with the sponsors' representatives and access to their promotional materials; and communication with clinicians. Parents frequently referenced the drug safety profile and results from animal studies.

All parents reported expecting some direct benefit of the drug, usually described as slowing or stabilizing progression of the disorder. Two parents described finding it difficult to manage their expectations.

I did my research so thoroughly that I was convinced that it was a cure. When you look at the information that they presented in the lab with the animals and stuff. (Father 107)

Well, I think we understood the benefits ... that the transcription process of the DNA would start working and read over the stop code and then he starts developing full-length dystrophin. As far as the actual, you know, what that would mean to him for his muscular ability, we really had no idea whether it would be dramatic or inconsequential. But if it would just mean he would at best get stronger or at a minimum at least maintain strength or something, yes. (Father 111)

Almost all parents hoped for significant improvement in strength, endurance, school performance, and/or quality of life. Many discussed the trial representing the possibility for a cure; while some believed this to be a reasonable hope, others identified it as overly optimistic. Parents further described the ability to have hope for improvement in their sons as an important secondary benefit.

I think we hoped that he'd be fixed. I mean the ultimate hope that this change with the skipping over his premature stop codon would instantly make him strong and that all his issues that are related to muscular dystrophy, the cognitive issues and everything would just disappear and, I think that's a little naïve. But that's the

big hope. So still, and I think as far as expectations go, we would have been happy with just knowing that he was going to retain some strength longer, and have some improvement on all fronts. (Mother 108)

Clinical investigators

Five of nine investigators reported starting the trial with expectations for some degree of improvement or stabilization of the disease course. Two investigators reported modest expectations and hopes based on past clinical trial experience. Several investigators reported that relationships with trial participants increased their hopes and described developing an emotional investment in the outcome. Three participants voiced retrospective concerns about having been too positive with the families.

I think that I allowed myself to get more optimistic then was warranted ... I was more emotionally ... invested in it than I had intended to be and was actually quite hopeful that we were going to get something ... The thing that I hope that I can do a better job of is kind of maintaining my equanimity more [during future studies]. (Investigator 2)

I was exceedingly hopeful that there would be some very positive outcomes. The [stop codon read-through] theory sounded great. And I thought that looking at the studies it was relatively safe. So I was actually hoping for a wonderful improvement in overall strength and stamina for the boys. (Investigator 6)

All of the investigators reported that the parents in their cohort expected benefit. Many found the degree of parental expectation and hopefulness concerning and difficult to manage.

I think the Duchene boys and the parents were hoping that it would slow the disease down so they would become Becker, and you know not go into a wheelchair at age 12, 10 to 12, I think that's what they were hoping. (Investigator 1)

The parents' expectations were unrealistic. They were hoping for a cure. They were sending information to one another. A 50/50 chance for improvement would have been more realistic. (Investigator 5)

Most of the clinicians referenced efforts that they took to help mitigate parents' expectations, but several voiced concerns that they did not do enough to promote reasonable expectations. Several clinicians described high 'DMD community' expectations that made it difficult to moderate their own expectations, as well as those of parents.

My concern on that front was more that we were raising expectations into the patient population ... We weren't keeping a lid on the expectations ... and I don't

know how you avoid it, and we all hope that we are not supposed to be coercive right, dealing with research subjects. I'm inherently coercive, that's just part of my scene, I mean whether I want to be or not. I mean it, the patients support us in that role ... we're supposed to be finding treatments for them. (Investigator 2)

I've seen this in many of the studies that we do. Their emotions get in the way. And when they hear 'experimental treatment', they only hear the 'treatment' part of it. (Investigator 3)

Motivations and decision making

Parents

Uniformly, parents' primary motivation for enrolling was the potential for benefit. Parents described a feeling of investment in the trial, excitement at being involved, and enthusiasm at having something to do to attempt to alter the disease course.

I was excited, I have to tell you. I was excited because I had another potential tool to help me with my son's disease. (Father 100)

Less than half of the parents mentioned altruism as one of their motives.

Any positive gain, you have to do it for the other boys coming up, you know? So you just – you feel committed ... you hope and pray that it could be with your boy, but if not, then future boys. (Father 107)

Most of the parents reported an easy decision or a 'non-decision' to join the clinical trial, that is, they never considered not enrolling their sons if they were accepted. However, parents also discussed their responsibility to understand the trial, specifically the risks and possible side effects. Few parents reported their clinician having a significant role in their decision making; rather, the clinicians supplied additional information and support. All of the parents perceived the risks as very low based on drug safety information. Even given the uncertain time during which we conducted the interviews, there was little evidence of decisional regret, except for wishing the children had fewer biopsies and blood draws. For most parents, the most difficult decisions related to managing the trial logistics and demands.

[The decision to participate] was a no-brainer. (Mother 109)

Most of the parents spoke knowledgeably about the drug mechanism of action and discussed feeling that the drug 'should work'. Many parents described positive attributes of their child's dystrophin

mutation, given its compatibility with the drug's mechanism of action. Several parents described feeling 'lucky' to have a child with the 'right' type of mutation for the trial. Several reported that their providers reinforced these perceptions.

To be honest I was so excited to have him have the possibility of a trial and I did not have a ton of concerns. At one point post diagnosis ... right after they found out that it was a stop mutation they said 'we've got the worse possible news, but the best within the worse possible news' and that 'there is this drug ...'. (Mother 112)

Clinical investigators

Most of the clinicians actively sought out an opportunity to participate as a trial site. It was gratifying and exciting to offer something other than standard management, especially given the disease course. Many clinicians were motivated by the novel, targeted approach of the drug.

It made me so excited. I thought it was a wonderful opportunity-history in the making! Working with the kids, it reminded me that I am a clinician primarily and that we were going through this together, sharing the intimate details of their lives. (Investigator 5)

All of the clinicians perceived that parents enrolled their children in hopes of benefit to the child.

I think that they ultimately believed that this was going to alter the course of their kids' disease ... there is no confusion on that for me, you know that was specifically stated to me over and over again. 'My son has to get in this study, I mean this is critical for him, we know he is fortunate to have an appropriate genetic cause, and you know if he doesn't get in the study, he's going to die'. And it didn't much matter what I said. (Investigator 2)

Pressures of a progressive disorder

Parents and investigators spoke about the pressures of a progressive, fatal disorder, and how these pressures played a role in decisions about and expectations of clinical trials. There were recurrent themes of 'time being the enemy' in DBMD. Parents felt a responsibility to participate in research before their children lost the ability to walk, and clinicians felt responsible for educating families about trials and offering participation. The ultimate pressure was knowing that 'doing nothing' was commensurate with accepting disease progression and early death.

Having Duchenne muscular dystrophy, it's all about the time. Once they are in a chair then everything goes downhill quickly for them far as their health ... I just

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started researching and wanted to be in [the trial] as quickly as I can, whether, you know – not even weighing out the bad side effects, 'cause I already know all the side effects [of DMD] for him. (Father 107)

Perceptions of benefits*Parents*

The parents delineated direct and indirect benefits of trial participation. All parents reported some degree of direct benefit for their boys, ranging from obvious improvements to subtle changes. These benefits included improved strength, endurance, and cognitive performance. A few parents described being unsure about whether there was benefit until they noted declines following the sudden end of access to the drug.

It felt like we had seen such tremendous improvement, we had no doubt in our mind that – that he was benefiting from it. (Mother 101)

I felt like he was working with me and he was stronger. He also felt that way ... And I said, well let's be cautious with this subjective type of measure ... about two weeks after he was off the medication he felt he got back to the stage before [the trial started]. So that gives a lot of confidence that the medication does have benefit. And we got the parameters like CK dropping and all these things. (Father 104)

The parents also described important secondary benefits including positive relationships with the study team and the psychological benefits of hopefulness and active engagement in an effort to change the course and outcome of DMD.

Clinical investigators

The clinical investigators described widespread parental perceptions of benefit; several reported that they also perceived benefit to cognitive performance or strength in certain patients.

Reactions to trial ending*Parents*

Parents reported anger, shock, and distress when the trial was stopped. The parents described feeling powerless and that they lost the hopefulness that the trial offered. The halt was sudden and unexpected. Parents expected such a sudden halt only if where there were drug safety concerns, which was not the case. Several parents were able to appreciate that 'these things happen' in clinical trials and it 'depends on the data'.

The trial had stopped and I was in a state of shock ... One minute you're participating in a study, you think you're making a difference, you think it's going along well and by the way, I'm kind of a skeptic but I really felt there was no question that this drug was having benefit for my son. (Father 100)

When he called up and said stop taking the medicine, I felt that conversation was worse than the diagnosis phone call when they told me he had muscular dystrophy ... hope goes a long way, and to take that from a family is just pretty devastating ... The shattering part was because it was his cure. (Father 107)

Almost all parents expressed a belief that the decision to stop the trial was also traumatic to the sponsoring company and the clinician investigators. Until the trial stopped, parents felt that they had a good relationship with the sponsor, with abundant communication and recognition of their important role in a team effort. At the termination of the trial, parents wished for more communication from the sponsor about decisions and the path forward. Some parents came to be impressed over time with the sponsor's willingness to engage the parents through advocacy forums. Other parents felt that the partnership between the sponsor and the parents totally broke down and that the sponsor no longer valued them.

Several parents noted the need to better prepare participants for the possibility of a trial ending abruptly.

I think I was never prepared that the trial would end. I never in my mind had thought that was even a remote possibility and I think that would be the advice that I would give [to other parents] to help to understand that the clinical trials is a not an FDA approved drug. Just because things look good doesn't necessarily mean that it's gonna end the way you think it's gonna end. And, you need to prepare yourself for that, or prepare your son for that too. (Mother 112)

Clinical investigators

The clinicians reported generally good experiences with the sponsor until the trial halted. Most investigators felt that the decision to stop the trial was abrupt, and the urgency was unnecessary given the lack of safety concerns. Many investigators felt that the company was evasive about the decision and wished that they had been consulted.

The investigators had the difficult role of informing families about the trial end and asking them to return the drug. Most clinicians reported having to manage the parents' shock and anger. Clinicians described that the negative effects of the trial ending were exacerbated by parent and DBMD community perceptions of drug benefit.

Well they think the low dose is working ... they never bought the negative results. And they are adamant to varying degrees that ataluren is still the best hope for their kids and that the FDA is not being fair and not allowing them to continue on with it, and PTC is not advocating it adequately for them ... And that was from absolutely day one, when this broke, we were just bombarded with complaints and concerns and a statement that this couldn't be true because our kids are doing so much better, this just has to be rectified, you are killing our kids. (Investigator 2)

Willingness to participate in another clinical trial

All but two parents reported that they would participate in a future clinical trial, citing one or more of the following: positive experiences during the ataluren trial, the psychological benefits of attempting to exert control over the disease course, and the psychological benefits of hope. Two parents were unsure and ascribed their uncertainty to the fact that their children had lost the ability to walk, limiting their eligibility for trials of interest. Several parents would pay more attention to the time commitment and logistics in a subsequent trial. Half of the participants spontaneously offered that they would 'do it all again'.

Relationships among stakeholders

An overarching theme was the importance of relationships and information sharing among the stakeholders. Parents and clinicians described the mutual importance of their relationships to the success of the trial and to psychological well-being.

They [the clinical trial team] were just so nice and so hopeful ... And they're family, you know. (Father 106)

We became almost like a family because we saw them so frequently and I saw them every time they came. And it was just not the boy's excitement, it's really the family's excitement I enjoyed, my experience with the families, their enthusiasm for this trial. (Investigator 4)

Parents noted that industry sponsors and clinicians should expect to have regular, organized communication with families. The parents were aware of and understanding about the communication restraints on the industry sponsors and appreciated that not all information could be shared. Similarly, many clinicians said that the sponsor should have consulted them more often; they felt that their perspectives and experiences would have proved valuable to the clinical trial.

Limitations

This was a pilot, retrospective study of experiences in one clinical trial. We were not able to recruit any

parents whose children received placebo, and thus, we have no ability to compare or contrast their views to those of parents whose children were on active drug. Although we had a good response rate from the clinical investigators, with 12 investigators from 15 sites participating, we did not achieve saturation on all of the topics. It is important to evaluate these data in light of the time when these interviews occurred – one of significant uncertainty and distress for many of the participants.

Conclusion

This pilot study describes complexities of an increasingly collaborative clinical trial experience for rare pediatric disorders. Although this is an exploratory study, the themes identified in this study have implications for sponsors, researchers, advocacy organizations, and families as they embark upon partnerships to facilitate the development of novel therapeutics. Before the ataluren trial was halted, it represented a successful effort toward mutual empowerment that reflected calls for increased participation in the research process by affected individuals, family members, and advocacy groups [18,19]. However, it is important to recognize differences in the values and motivations of the stakeholders [20], including industry, scientists, clinicians, and patients who must work together to uphold the integrity of the clinical trial. Differing interests became striking during and after the trial termination, when parents and clinicians reported a loss of power and control that was distressing and confusing.

Parent participants displayed remarkable knowledge of the drug under trial and the clinical trial process. Yet, overall, they were not prepared for the most likely outcome of any clinical trial – a failure to show the required effect on the primary study endpoint. This study highlights a need for renewed emphasis on education about, and psychological support for, a unsuccessful trial and the resulting loss of access to the drug.

The parents' decision making about trial participation was driven by the progressive nature of the disorder. Although parent expectations were high and they hoped for a cure, their expectations should be interpreted in light of the importance of hope and the powerful feelings associated with being able to engage in active efforts to affect the disease course. Unlike the findings of Garralda *et al.* [16], there was suggestion of therapeutic misconception among the parents, in that parents generally described the study in terms of individual benefit rather than an effort to gain generalizable knowledge. Yet, the parents' focus on individual benefit seemed to reflect

emotional engagement rather than a misunderstanding of the trial goals, suggesting a dissonance between their cognitive understanding and emotional representation of the trial. The parents' emotional investment resulted in notable therapeutic optimism and misestimation.

We also found evidence of therapeutic misestimation in the clinician population. The investigators were in the difficult position of having to monitor and manage the expectations and hopes of the participants. Several clinicians worried about their own involvement in increasing parents' expectations during the trial. Yet the parents reported that their expectations originated primarily from sources other than the clinicians – notably, the sponsor and the 'community'. This assertion should be cautiously interpreted given the retrospective nature of the study and the multifaceted and subconscious nature of variables that contribute to expectations. The effect of overly optimistic advocacy communities on DBMD clinical trial participants has been raised by Woods *et al.* [21], who suggest that a 'collective therapeutic misconception' may be propagated by neuromuscular disorder advocacy organizations to patients and families.

This study reinforces the importance of engaging clinical trial participants or their proxy decision makers around both expectations and hopes to achieve a more measured understanding of decision making and therapeutic optimism. Our results support those of Jansen *et al.* [22], who found that participants showed optimistic bias related to benefit but less so related to cure. Our participants had high expectations for benefit, but most were able to differentiate between those high expectations and their hopes for a cure.

The interviews suggest that the mechanism of action of the drug under trial may have increased expectations for some parents and clinicians. Henderson *et al.*'s [7] data suggest that subjects' impressions of technical aspects of the intervention may affect expectations and lead to therapeutic misconception. This is specifically relevant to the DBMD community, as several other mutation-specific therapies are under trial or in pre-clinical development.

A central theme was the importance of the highly valued 'family-like' relationships that developed between the participants and the study site teams. Similarly, Kost *et al.* [2] found that the factor most associated with a positive view of the research experience was developing a close relationship with the study team. In this study, the benefits of close relationships were a group of engaged, committed participants who took their trial participation seriously and had great trust in the study team, and a group of engaged, committed clinicians who were eager to be involved in clinical trials and recruit patients with a true hope of benefit. These

relationships were especially important to participants when their perceived control or feelings of empowerment were threatened. Possible downsides of the close relationships may be inaccurately enhancing the expectations and hopes of parents and some of the clinician investigators, and insufficient emotional distance between the clinicians and the families involved in this study. Parent-clinician relationships may provide an ideal intervention point for efforts to improve participant and family well-being related to clinical trial participation.

Future research that includes a broader range of clinical trials is needed to better understand motivations, expectations, hopes, and how benefits are defined and valued in pediatric clinical trials for progressive, fatal disorders. These studies may explore the associations among perceived vulnerability, control, and stakeholder relationships and roles. Data from future studies may also inform important ethical considerations about benefit-risk determinations (e.g., the extent to which family-clinician relationships within a clinical trial context should be considered as secondary benefits). Ultimately, such research may further inform ways to maintain the benefits of an enmeshed clinical trial community while minimizing the associated risks.

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Conflict of interest

The authors have no conflicts to disclose. During the course of this study, the first author (H.P.) became an employee of Parent Project Muscular Dystrophy. H.P.'s role in this study was under the auspices of a Professional Services Contract as a Guest Researcher with NHGRI.

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