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Parents' experience
of benefits and
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Duchenne muscular
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trials

CHAPTER 7.

Parents' experience of benefits and burden during Duchenne muscular dystrophy clinical trials

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ABSTRACT

Objective: Little is known about how parents who consented to children's participation experience benefits and burdens during clinical trials. This understanding may facilitate informed consent and maintain participation.

Methods: Using interviews, we explored benefit/burden assessments of parents of children with Duchenne muscular dystrophy (DMD) during and after trials.

Results: Fifteen parents described a complex, dynamic process of defining, evaluating, and assessing "net benefit". Most parents perceived direct DMD-related benefits. They monitored for benefits but felt hampered without trial data and due to DMD's progressive course. Participants expressed frustration that outcome measures did not reflect outcomes of importance. Other perceived benefits included altruism, close relationships with the research team, and optimism. Burden was variable across trials, including time and travel, financial impact, insufficient communication, and clinical procedures.

Conclusions: Our results suggest the importance of a reasonable match between parents' expected and experienced benefits. Parent decision-makers may be particularly motivated to perceive benefits to justify exposing children to burden and risks. Dynamic benefit-risk assessment resulted in sufficient motivation to remain in the trial even when participation was burdensome. With rare disorders such as DMD, recruitment and retention concerns are especially relevant and must be balanced against feasible, unbiased, and yet permissive trials.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a recessive degenerative muscular disease that occurs in approximately 1 in 3,500 males.¹ On average, diagnosis occurs at age 5 with loss of ambulation occurring between the ages of 7 and 13.² The average life expectancy is in the late 20s.³ Those affected and their caregivers face significant burden related to disease progression, ongoing care demands, and financial impact.⁴⁻⁷ There is no cure for DMD, nor are there any FDA-approved therapies.² However, there are several potential treatments that are currently being studied in clinical trials and others in pre-clinical development.⁸

Caregivers may look to these new potential treatments as a way to maintain optimism when faced with a progressive, fatal disorder,⁹⁻¹¹ and caregivers whose children are enrolled in trials may be motivated by hope for the potential benefits these trials offer.⁹ Clinical trials for DMD

provide a complex and compelling model for exploring perceived trial benefit through the lens of a parent proxy decision maker.

A number of studies focused on a range of pediatric disorders have examined aspects of caregivers' perceived benefits of pediatric trials. Many of these studies focus on the role of expected or anticipated benefits as one of the variables influencing a caregiver's decision to allow his or her child to participate in a trial.^{12,13} Few studies have collected data during the course of the study or after it concluded to examine participants' perception of the benefits actually obtained.^{14,15} As a result, we know little about how participants experience and value the benefits of participating in a trial. This study was designed to better understand and define meaningful trial benefits and how parent decision-makers balance benefits and burden. Understanding how benefits are weighed against burden during the course of a trial may inform efforts to achieve patient-centered drug development and reduce trial withdrawal rates. These are issues that may be particularly relevant for rare disorders, which may have strong disorder communities but limited numbers of potential trial participants.

METHODS

This study employed a community-based participatory research approach, in which stakeholders contributed their expertise, as equal partners, to explore an issue of importance to the community and integrate the knowledge gained with action to benefit the community involved.¹⁶ A multi-stakeholder research advisory team led the study. All major decisions during the course of the study, including development of the study protocol, study processes, development of the interview guides, and the thematic interpretation were made by the research advisory team.

The participants were parents of sons with DMD who were currently involved in, or who had taken part in, a clinical trial within the past three years in the United States or Canada. Participants were at least eighteen years of age and able to complete an interview in English. Parents who participated in a previous pilot study⁹ were excluded from this study. Participants were recruited through an advocacy organization, a patient registry, and using snowball recruiting. They were invited to participate in an interview to discuss their trial expectations and experiences. We continued recruitment and interviewing until we achieved saturation (i.e., information redundancy) on our topics of primary interest.

The study design was an exploratory qualitative study using semi-structured interviews. The interview topics included trial expectations and hopes, decision-making, experiences in the trial, and perceived benefits; only the latter are reported here. The interviews were conducted between June and October, 2012 and averaged approximately 50 minutes.

Two independent investigators (HS and HLP) used NVivo 9 QSR, a qualitative analysis software package, to code responses. Inter-coder agreement was above 90% and discrepancies in the coding were discussed to clarify codes, identify true differences in interpretation, and facilitate reconciliation. All analyses were based on consensus codes. We conducted thematic analysis within the parent group, with attention to differences in themes based on the trial in which participants were involved. Coded passages and emerging themes were explored and categorized by the Research Advisory Group. Major themes that arose from the analysis and illustrative quotes are presented.

This study was approved by the Western Institutional Review Board.

RESULTS

Participants

A total of thirteen mothers and two fathers of children with DMD, representing participation in six clinical trials, participated in the interview study. All participants' children had DMD, and their ages ranged from six to fifteen. Eleven children participated in trials of novel, mutation-specific drugs that aim to alter the dystrophin protein product; two in trials of other novel drugs that target secondary effects of the disease; and two in trials of drugs previously-approved for other indications that target secondary effects. Nine parents reported that their children were on active compound; three did not know; and four reported knowing or suspecting that their child had been on or was currently receiving placebo. Most participants' children were still enrolled in the trial. Three were involved in an extension study, two in a trial that had ended, and two were unsure of the trial status. We do not provide additional details about participants because of the risk of identification in a rare disease trial.

Trial Experience Themes

The interviews explored parents' experience of trial participation through questioning about perceived benefits, burden, and risks or threats of participation. Parents' descriptions of the

experience of the clinical trial included multi-dimensional discussions of the benefits of participation—**defining** ways the child and family benefited; how benefit was **measured or evaluated**; and how benefit was **valued** against burden and risk.

Defining the Benefits of Clinical Trial Participation

Direct benefit to the child

When asked to describe their clinical trial experience, most participants reported direct benefits to the child. Parents defined direct benefits as stabilization or slowing of disease progression; acquiring new motor skills; improved cardiac outcomes; and/or quality-of-life improvements such as more energy. For all but two parents, benefit to the child was described as the key motivator for maintaining their child's enrollment in the trial.

When asked about specific benefits of trial participation:

- Five parents noticed new motor skills in their children that they attributed to the study drug. These parents were confident in their appraisal of physical benefit to their child.
- Eight perceived that their child's disease progression had stabilized or slowed (six described motor stabilization and two described cardiac stabilization). Two parents noted declines after the child was taken off the drug, which reinforced their perception that the drug caused stabilization. Most of these parents expressed somewhat less confidence in their perceptions of benefit than the five parents who noticed new motor skills.
- Two perceived that the child did not receive physical benefit. One parent, who reported that his/her child started on placebo, explained that all participants had crossed over to active drug, and thus the parent was still expecting some benefit. The other felt the child had not and would not receive any physical benefit.

Access to the Experimental Drug

Access to the experimental drug was considered a trial benefit. The majority of parents expected a successful trial outcome and continued access to the experimental drug. Those who participated longer or whose participation was complete described that initial optimistic expectations of trial success were somewhat tempered over time. Several found their expectations for a continued drug access threatened by unfilled trials, safety concerns, and perceived problems with appropriate blinding. Participants who became more pessimistic about

the long-term access to the drug tested in their trial, however, remained optimistic about other DMD trials' chances of success.

Relationships with the Trial Team

The large majority of parents reported close relationships with members of the clinical trial team as an important benefit to the family. The relationships were described not only as an ancillary benefit to the child due to enhanced access to medical expertise, but also as a primary psychological and tangible benefit to the parents.

"It just means a lot that it seems personal to them. They seem to really care, and really hope that this works. And again, not only does that hope kind of spill over to you a little bit, but there's just something about the fact that someone that is not related to you cares...And it makes you, you're kind of endeared to those people because they seem to care so much.... I'm like, 'we would do anything that you guys would ask of us, because you guys have made this a great experience.'" Parent 100

The close relationships represented being more than "just a number" and the clinicians having a high level of commitment to the children. Four parents described systematically seeking out and nurturing these relationships to extend or increase the benefits.

"I've developed very close friendships with most of the staff that we see...I'm extremely proactive, I make a point of trying to build friendships with these people outside of clinic because now we're kind of friends they tell me things that [they wouldn't] if they only saw me twice a year and I made no effort in-between...I know these people, I know their families, you know I correspond with them personally outside of you know their job...I've been very fortunate that certainly we as parents are not left in the dark and they've been very accommodating...but only so because of the type of parents we are, like I said if I were somebody that just showed up to clinic and left...you'd know nothing, it's because I've really gone out of my way to stay on top of things, and I want these people to look at us, not just as patients, but as part of their social circle." Parent 105

Parents valued close relationships that made them feel appreciated and improved their access to clinical expertise and information about the trial; for some parents this resulted in conflicting desires to have informal social relationships with investigators while concurrently admiring their

professional persona. In parallel, parents described the relationships leading them to be strongly committed to the clinical trial team and by extension, the clinical trial.

Psychosocial benefits of the clinical trial

Parents described several psychosocial benefits to the family (the parents and the child). Almost all parents reported psychological benefits of active efforts to intervene in the progressive disease course; positive feelings associated with altruism; an enhanced sense of optimism; and enjoying the significant “together time” required by participation. Four described social benefits to their children based on interactions with other children with DMD through the trial.

Evolving definitions of perceived trial benefits

Half of the parents described changes to their priorities and expectations during the course of the clinical trial that impacted their perception of benefits. These changes came from external sources (e.g., short-term or permanent loss of access to the drug) and/or from disease progression in the affected child (e.g., loss of ambulation). As a result, parents described adapting over the course of the trial to focus more on altruistic reasons for participating and/or ancillary benefits. Several of these parents described exploring options for a new clinical trial that might provide more direct benefit.

Evaluating for Benefits during Clinical Trial Participation

Many parents undertook systematic efforts to evaluate for benefit of clinical trial participation.

“When he was doing his six-minute walk test, for example, I was timing it. I was counting how far he was going from test-to-test, to see, is he going further? Is he stronger? And so I was kind of monitoring [him] myself, to see if there was improvement.” Parent 111

Several parents were wary of the effect of their strong desire for benefit on their ability to be objective, and tried to balance being as neutral as possible, tempering expectations, and maintaining optimism.

“I think as a parent, psychologically, you just want to see something. And so I would watch him and I'd be, like, ‘Did I just see that? Is that new?’ I was driving myself crazy to the point you actually have to remove yourself a little bit. Because you want to see something so badly...at one point I was, like, Okay, we're participating in this, I have to stop looking for signs.” Parent 118

Most parents described that other people directly aided them in their evaluation efforts and/or supported their impressions: healthcare providers not involved in the trial, relatives, teachers, and other parents of individuals with DMD. However, their evaluation efforts were complicated by the natural history of DMD, since DMD has significant phenotypic heterogeneity and includes normal plateaus and losses. Parents felt that their ability to monitor their child for benefit was challenged by not receiving clinical data during or after the trial.

Many parents expressed frustration with the trial outcomes and measurements. They reported that parents and professionals look at benefit differently, and care about different outcomes.

“I think to [professionals] an improvement just means that the muscle, I don't know, reacts faster or doesn't deteriorate as quickly. I don't think they often think about the day-to-day benefits to [my son] and his self-esteem and quality of life.” Parent 115

Similarly, several parents who perceived benefit were frustrated by their inability to convince the clinical trial team and sponsors.

“There's no way for us to prove to them how much better he's doing in his daily life... it's been frustrating a little bit when they tell us they're not sure that it has benefit and we are sure that it does.” Parent 104

The Valuing of Benefits during Clinical Trial Participation

Placing value on the trial experience appeared to be a dynamic process, where the perceived benefits were weighed against the **trial burden**; potential for **side effects and harms**; and perceived **likelihood of trial success**. Though negatives of trial participation are described below, most participants did not express decisional regret, and the experience of trial participation appeared to be highly valued by more than half of the participants. Even participants who were less positive still placed positive values on the experience that included altruistic perceptions of being part of something “bigger” that would lead to benefits to the community. Many parents perceived a responsibility to maintain the trial's integrity, and felt that there should be reciprocal benefits— that is, benefits to the child from the trial, and to the trial from the child's participation.

“... you're part of a bigger system and you've got to be protective of the study. And I think that's the difference. But it's not just about you and your child and your doctor anymore. It's you, your child, the doctor, and the study.” Parent 101

Trial burden

Although parents' perceptions of trial burden varied by trial, common themes related to time requirements, travel burden, and insufficient communication. Parents noted specific burdens that were serious enough to threaten their continued participation in the trial that included financial pressures; poor communication from the sponsor during the trial; lack of social support; perceiving the child to be on placebo; and lack of perceived trial benefit to the child.

Overall, one of the trials was described as more burdensome than the others. Most parents perceived the time and travel requirements as burdensome, but many reported being prepared for these burdens and adapting to them during the course of the trial. Most parents described a negative impact of the trial time and travel burden on their ability to work or their work performance. Three described significantly more time burden on the family than expected, and three others felt that the duration of their trial experience was longer than expected.

Insufficient communication with the sponsor (for most parents) and study sites (for three parents) added to the trial burden, and in several cases threatened the willingness of parents to keep their children enrolled in the trial. Parent interviewees expressed discomfort that communication with other participating families was “against the rules.” (The informed consents of several trials represented in this study required that participants not share information about their trial experience with peers.) All interviewees described some communication with other families during the trial, though several described these discussions as guarded or limited in scope, especially related to comparisons of assumed trial randomization and perceived benefit. Most parents who recognized a significant physical benefit for their child described some associated guilt.

“There was communication [with other families in the trial], but...we were just very guarded in how we responded...when people said, do you see any difference in <child's name removed> ...it was sort of like, oh yeah, maybe, but we're not sure, even though inside ourselves we knew we were seeing a difference, and we were pretty sure he was

*on the high dose of the meds...we didn't really share that with anybody else in the trial.”
Parent 104*

Most parents (10) felt that communication with other participant families about the trial experience made it a more positive experience and helped with evaluation of benefit.

“It's just nice to have someone else that knows what you're going through. ... And it was just interesting, because you know how your experience was, and the things that you noticed, and you wonder all the time, are other people noticing this? Is someone else noticing this little bitty thing, or is it just me? Or am I trying to read into something that's not there because I want it to be working?” Parent 100

Four parents voiced a need for a safe and ‘legal’ environment for participant families to interact with each other, perhaps moderated by a professional who would correct misinformation and clarify confusion.

Other burdens described were financial burden due to disrupted work schedules and/or unreimbursed travel costs (a very significant burden for a subset of participants), overly-rigid protocols, placebo randomization, and difficult interactions with contract research organizations. Several parents were frustrated at not understanding the trial timeline, which challenged their motivation to stay involved; this was especially true of parents who perceived limited benefit, who wanted to know that “an end was in sight.” A few participants who perceived the greatest burden also expressed disappointment that the study failed to meet their expectations in other ways as well; this subset reported that the benefits of study participation were not perceived as outweighing the burden and they had considered withdrawing from the study.

Most parents felt there was minimal to moderate burden to the child participating, with the exception of the muscle biopsies that were required in some trials and considered a significant burden. In general, most parents perceived the trial to be a positive or neutral experience for the child.

Side effects and harms

Though parents perceived low and manageable trial risks, they continued to be alert for potential harms during the course of the trial. They describe being vigilant for: specific risks and side effects thought to be associated with the drug; exacerbation or progression of DMD

symptoms; and more general threats to the child's quality of life. The side effects they reported their children experiencing included weight gain, feeling sick to the stomach, having erections, and skin reactions. In studies involving muscle biopsy, the procedure was perceived as considerably burdensome to the child. Two participants felt strongly that their child being randomized to placebo was a harm.

Several parents described being most concerned about potential risks after the decision-making process, especially during the early part of the trial. For most of the parents, ongoing perceptions of minimal risk motivated them to remain engaged in the trial. Most families agreed that the only thing that would prompt them to withdraw their child from the study were serious side effects or pain.

ASSESSMENT OF NET BENEFIT

After defining meaningful benefits, evaluating for those benefits during the trial, and valuing benefits versus risks, parents came to an overall assessment of net trial benefit. Parents represented this assessment of net benefit as a dynamic process of coping with choosing to put the child in a trial, and their associated psychological need to have a meaningful experience for the child. The assessment of net benefit was described as a parental responsibility. Further, parents described feeling that it was their responsibility to navigate the trial risk and processes so the child had access to benefits, in several cases against the expressed wishes of the child.

"At one point <child's name removed> looked at me when he was getting an injection, and he said, 'Promise me once this trial is over, you won't make me go in any other clinical trials.'...That night, I said to him, 'Do you remember you asked me that question? If this clinical trial doesn't work, or it does work and there's another clinical trial that comes up that we think might help you, I will want to do it because as far as I'm concerned, I'm never giving up. If I think there's something that can help you, I can't promise you that I'm not going to try it, even if it's hard, even if it's painful because that's my job.'" Parent 101

DISCUSSION

There are few studies that explore parent decision-makers' perceptions of the accrual of benefits and burden during or after the course of the trial. In this study, which extends a pilot

study of parents in one Duchenne trial,⁹ participants described a complex and dynamic process of defining, evaluating, and assessing the value of benefits as an ongoing process of coping with their decision to enroll their child in a DMD clinical trial. Though primary benefits to children were the most valued, psychosocial benefits to the family and close relationships with the clinical site teams were also important. Assessment of benefit changed as children progressed in their disease, as trials advanced, and as aggregate trial data became available. Specifically, parents described focusing more on altruistic benefits over time, apparently reflecting an effort to cope with a “shifting reality” about the trial and child’s prognosis.

Parents represented dynamic efforts to manage the decision to enroll their child in a clinical trial and maintain a child’s participation that reflected their need for a meaningful trial experience. The process and outcome of assessing trial “net benefit” is important to understand, because perceived benefit was described as a motivation to stay involved in the study, even when participation was burdensome. It is in the best interest of all stakeholders to encourage a match between expected and perceived benefits to maintain trial participation, sustain participants’/caregivers’ feeling of responsibility to the trial, and promote family wellbeing. A key component of that match is in how benefits are understood prior to decision making and during informed consent. Nancy King¹⁷ describes a compelling need to promote more reasoned discussion about potential trial benefits by distinguishing different types of benefits as well as the associated dimensions: nature, magnitude, and likelihood. Findings like ours promote the ability of researchers and regulators to improve informed consent by framing types of potential benefits congruent with how participants may experience them, while also striving to quantify the associated dimensions of benefit.

This study suggests one common point of mismatch in a clinical trial—between clinical outcomes defined by the trial sponsor and the quality-of-life related benefits that parents value, and for which they evaluate their child during the course of the trial. While it is important for sponsors and clinician investigators to reinforce the reasoning behind choosing specific trial outcomes, researchers should anticipate and address the parents’ frustration in this regard. Based on our study, we would expect less discrepancy in trial outcomes that directly reflect the child’s quality of life. Adding an additional dimension to King’s recommendations¹⁷ about describing benefit, how benefits are ascertained and measured, may assist potential

participants in anticipating mismatch while also facilitating their understanding about which benefits “count” toward a successful trial outcome.

To some extent, the trial burden described by our participants could be reduced to improve the benefit/burden balance. Clear targets for improvements in communication and social support for participating families were evident. Parents were uncomfortable with the prohibition present in several of the studies against sharing their trial experiences with others, which limited their ability to receive and give support. Parents described the need for more communication and support about the trial processes and outcomes, especially in the context of logistically and emotionally-challenging trials. Efforts to facilitate and encourage appropriate peer communication and social support related to trial participation might reduce an individual parent’s mismatch between expected and perceived benefits through the peer group process of defining “reasonable” expectations for benefit during the course of the trial.

Many of the aspects that challenged parents’ perceptions of trial benefit were largely outside of the control of the sponsor, including lack of benefit to the child, overall drug efficacy, and loss of drug access during the course of the trial. In cases of challenges outside of their control, sponsors might build upon the strong relationships between participating families and clinical site teams to facilitate anticipatory guidance during informed consent and the course of the study, and site team communication and support in the case of an adverse outcome. In our study, the relationships between parents and clinical teams impacted the evaluation of trial burden and benefits and appeared important to maintaining trial participation.

LIMITATIONS

The primary limitation is that parents interviewed represent “first adopters” of clinical trials for Duchenne muscular dystrophy and their experiences and perceptions may differ from other parents of children with DMD. There is also a potential for bias in reporting perceived benefits due to the high emotion associated with many of our interview topics.

CONCLUSION

Though DMD represents a complex clinical trial situation, there is no reason to assume that the

themes identified here are unique. Major themes that emerged from this study may be especially relevant to other progressive pediatric disorders. Parent decision-makers may be particularly motivated by the chance for their child's benefit and trial success, which may help justify decisions to expose the child to burden and risks. For rare disorders, issues of adequate recruitment and retention are especially relevant and must be balanced against feasible, unbiased, and yet permissive trials. While high perceived benefit likely keeps families engaged and enthusiastic about trial participation, the downside is that if those perceived benefits are not realized with an approved drug, it may lead to serious challenges to the wellbeing of families.

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