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Consent for clinical trials: challenges of decision making for a progressive pediatric disorder

CHAPTER 8.

Consent for Clinical Trials: Challenges of Decision Making for a Progressive Pediatric Disorder

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ABSTRACT

Objective: This interview study explored parents' deliberation and decision making about children's participation in Duchenne muscular dystrophy (DMD) clinical trials.

Methods: Semi-structured interviews conducted with parents and clinicians in U.S. or Canada were assessed using thematic analysis.

Results: Fifteen parents involved in six trials and eleven clinicians involved in ten trials were interviewed. Parents described benefit-risk assessments using information from advocacy, peers, scientists, clinicians, and sponsor materials. Strong influence was attributed to the progressive nature of DMD. Few considered the possibility of trial failure. Most made decisions to participate before the informed consent process, but none-the-less perceived making an informed choice with little to lose for potential gain.

Clinicians described more influence on parental decisions than attributed by parents. Clinicians felt responsible to facilitate informed decisions while maintaining hope. Both clinicians and parents reported criticisms about the informed consent process and regulatory barriers.

Conclusions: The majority of parents described deliberation processes leading to informed choices that offered psychological and potential disease benefits. Anticipatory guidance about the potential for trial failure might facilitate parents' deliberations while aiding clinicians in moderating overly-optimistic motivations. Regulators and industry should appreciate special challenges in progressive pediatric disorders, where doing nothing was equated with doing harm.

INTRODUCTION

Clinician investigators and clinical trial sponsors benefit from an awareness of motivations to participate in trials and participants' decision making processes.[1] A unique aspect of pediatric clinical trials is that parents and caregivers make choices on behalf of their children, and the values and beliefs underlying proxy decision making may not be the same as for adults deciding about their own participation.[2] As such, investigators aim to facilitate informed parental decision making in pediatric trials.

Elwyn and Miron-Shatz (2009) describe decision making as a process of pre-decision deliberation followed by the act of making the determination.[3] Deliberation includes obtaining information and appraising one's own knowledge, imagining alternative outcomes, predicting

one's emotional state in the future, and constructing preferences about the decision.[3] Determination is coming to an intention to enact the decision.[3]

Based on existing research, the deliberation process for parents consenting to their child's participation may be represented by weighing perceived benefits against risks.[4] Perceived benefits have been found to include access to new treatments;[4,5] treatment at no cost;[4] access to the best treatment options;[4] increased hopefulness;[4] the ability to help others; and increased knowledge.[4,5] Perceived harms included randomization; and time demands and general inconveniences.[4]

A pilot study of one clinical trial for Duchenne muscular dystrophy (DMD) found that expectations for individual benefit drove the deliberation process, and parents described strong pressures to enroll their children due to the illness trajectory.[6] DMD is a rare neuromuscular disorder that causes progressive muscle weakness and death typically in the late 20s.[7,8] There are no Food and Drug Administration approved therapies, but many potential therapeutic approaches are in clinical trial.[9] Extending the scope and depth of the pilot, this study explored decision making deliberation and determination of parents who consented to a range of DMD trials for their sons, as well as the perspectives of clinicians on clinical trial teams. The overall study objective was to identify potential intervention targets to improve informed decision making and wellbeing in families living with DMD.

METHODS

This retrospective, explorative qualitative study was guided by a Research Advisory Group using a community-based participatory research (CBPR) approach, a process by which stakeholders act as equal partners to identify and explore a phenomenon of importance to the stakeholder community.[10] Semi-structured interviews with clinicians and parents were conducted between June and October, 2012. Both sets of interviews averaged approximately 50 minutes. Parent participants had sons with DMD who participated in a trial within the past three years in the United States or Canada; participants in the previous pilot study[6] were excluded. Participants had to be at least 18 years of age and able to complete an interview in English. The second group comprised clinicians active in DMD trial teams over the past three

years. One clinician also participated in the pilot study;[6] that clinician was a principal investigator on more than one trial and he/she discussed other trial(s) for this interview.

Both groups were recruited through an advocacy organization, a patient registry and the associated provider portal, and using snowball recruiting. They were invited to participate in an interview to discuss clinical trial expectations, decision making and experiences; only decision making is described here.

Two independent investigators (HS and HLP) developed the research codebook and used NVivo 9 QSR software to code responses. Inter-coder agreement was above 90% and discrepancies in the coding were discussed to promote reconciliation. We then conducted thematic analysis within and between the parent group and the clinician group. Emerging themes and representative, de-identified coded passages were explored and categorized by the Research Advisory Group. This study was approved by the Western Institutional Review Board.

RESULTS

Fifteen parents of children diagnosed with DMD and eleven clinicians participated in the interviews. Information about the participants can be found in Table I.

Table I: Demographics of parent and clinician participants

Parent Participants (15)				
Role	**Child ages**	**Trial type**	**# Trials represented**	**Trial status**
Mothers (13) Fathers (2)	6-15 years	Novel, mutation-specific drugs (11) Other novel drugs that target secondary effects (2) Previously-approved drugs for other indications (2)	6	Child still enrolled in trial (8) Extension trial (3) Trial ended (2) Unsure of trial status (2)
Clinician Participants (11)				
Role		**Trial type**	**# Trials represented**	**Clinician status**
Physicians (5) Study coordinators (3) Physical therapists (3)		Novel, mutation-specific drugs (9) Previously-approved drugs for other indications (6) Supplements (2)	10	Current or previous trial PI (6) Non-PI trial team member (5)

The trials represented included a mix of placebo-controlled and non-randomized trials. 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. The clinician participants represented a range of experience, from less than 10 years (three) to more than 20 years (four).
All of the participants completed the entire interview.

Parents' Deliberation Process
The interviewer asked parent participants to think back and describe their decision-making process.

Obtaining information
During the deliberative process, parents obtained information about clinical trials from advocacy groups and advocacy conferences; sponsor websites and materials; professionals involved in the research; other parents; outside professionals perceived as impartial; the child's clinician; and scientific publications. Five participants described first hearing about the clinical trial from their child's healthcare team, but only one parent described decision making based predominantly on information from their child's clinician.

Most parents described clinician investigators as objective, realistic, and honest. Few parents attributed decision-making pressures to their healthcare providers. Three parents encountered clinicians who they described as too enthusiastic; i.e., whose hope and enthusiasm about the trial encouraged high expectations from the parents. Two parents experienced "over-selling" of the clinical trials during communications with sponsors or sponsors' representatives.

Participants described the informed consent (IC) process as minimally or not at all important to their decision making; that is, they informed themselves and made their determination to enroll their children before they engaged in the IC process. However, parents learned new information about the study processes and logistics during IC, and most positively described the consent discussions as extremely detailed about the timeline and procedures. On the other hand, the IC documents were frequently described as too long, difficult to read, and technical; and the key information was difficult to prioritize and remember.

Managing decision pressures

All parents described emotional, time-related pressures due to the progressive and fatal nature of DMD, including the child permanently losing abilities and missing a limited window of trial eligibility. Several described additional pressures of having to choose when children qualified for more than one trial. Most parents expressed distress about the long wait required for drug approval, which was perceived to be primarily due to unnecessary regulatory barriers and industry delays. This had enhanced salience because parents expected that treatment benefits may be reduced as the disease progressed.

> *"I'm sitting here watching time tick by knowing that every month that goes by, my kid is less likely to be able to take advantage of this drug if it does work. And I find it excruciating and unconscionable." Parent 101*

Assessment of potential benefits and risks

Parents felt that undertaking a benefit/risk assessment was a requirement for making a "good" decision. Parents described the importance of doing research and understanding possible risks and side effects. Nine parents expected specific, defined physical benefits to their child as they were making their clinical trial decisions; most were participants in mutation-specific trials. Five described more general expectations for some type of individual benefit to the child. Only one participant consistently conveyed no expectation for individual benefit.

All participants described optimistic hopes for a better outcome for their child, as well as hopes for a successful trial outcome. Though most participants reported altruistic influences on their decision making and a feeling of responsibility to participate, few described these as influential motivators in their assessment of potential trial benefits.

The widespread perception of low or manageable risks associated with all of the trials played a large role in parents' decision making. However, a few parents described being frightened by potential side effects, and seven parents worried about allowing their child to be a "guinea pig" or to be used as a means to an end. Many parents addressed conflicting desires to have immediate access to experimental drugs, willingness to accept risk, and concerns about risks and side effects. This conflict was less commonly described by parents making decisions about previously-approved drugs, where the risk/side effect profile was perceived to be well known.

“I want to avoid getting hurt badly with something that's rushed too fast. I don't know what the right answer is, but it's balancing that being a hundred percent sure versus trying. We're running out time. I know the clock ticking.” Parent 111

Half of the parents involved in placebo-controlled trials considered the potential to be randomized to the placebo arm as an overt risk of participating. Several perceived the most significant risk as a threat to the child’s quality of life due to trial burden.

Rarely-described deliberation factors

Notably, only a few parents worried about a failed trial or loss of drug access while making trial decisions, and none as a major decision-making factor. Few parents described trial logistics, processes, or demands on their families as a significant part of their decision making. Only two parents reported considering barriers to eligibility for other trials due to participating in the trial.

Parents’ Decision Determination

For most participants, the result of the benefit/risk assessment was that they had little to lose for potential gain, and thus decision making was described as relatively straightforward. Only two participants described their decision as anything other than an “obviously right” choice. Parents reported psychosocial benefits to their determination that included increased optimism and a feeling of empowerment to impact the progressive disease course.

Some parents made a determination to participate in a trial and then searched among available studies, while others described making a determination to target one specific trial. In both cases parents viewed their decisions as rational and felt themselves to be educated decision makers. Though several parents felt that they did not have access to all of the information that they wanted to make fully informed decisions, such as earlier-phase trial data, participants demonstrated being well informed about the objectives of clinical trials in general, as well as their specific trial. Most participants made statements alluding to an understanding of the goal of clinical trials (obtaining generalizable knowledge and better understanding DMD), and in no cases did their decision making seem to stem from a misunderstanding about the purpose of clinical trials.

Clinicians' Role in Parental Decision Making

Clinician Perspective: Their Responsibility in Decision Making

Clinicians reported feeling responsible for allowing parents to maintain their enthusiasm and hope, while also helping them make determinations based on realistic expectations of the study processes and likely outcomes. They were challenged to find the right balance among protecting families, acting in their best interest, and fostering a successful trial. Clinicians aimed to use the clinician/patient relationship to protect families and help them make good decisions. Three clinicians further stated that the relationship between the family and the investigator was the primary reason for parents' decisions to consent; parents want to please clinicians and meet their expectations.

Clinician Perspective: Information Communication

All clinicians described trial education as important for deliberation, for reducing decisional regret, and keeping families in the trial long term. Specific educational topics that they strove to integrate into parents' deliberation included: trial processes, time commitment and burden; the chance of the trial ending early; understanding the implications of a placebo-controlled trial; understanding equipoise; the proposed mechanism of drug action; early phase data; potential side effects and harms; how to assess benefit and risk; trial eligibility; and effects of participating on eligibility for future phases/trials. Clinicians reported several factors that constrained them in their educational roles: concerns about the public's ability to interpret complex information; the length/complexity of required information in the informed consent; institutional or sponsor constraints in what they were permitted to tell parents; lack of access to proprietary information needed to facilitate informed choices; and having to counter-act overly optimistic messages from trial sponsors.

Clinicians also reported barriers in their communication with families interested in trials. Seven described a disconnect between what they say and what families hear, such as parents not wanting to hear about risks or ignoring discussions of trial burden. On the other hand, clinicians described some parents as having negative reactions to receiving incomplete information about the potential drug, even though such limitations are inherent to a trial. Many clinicians expressed a preference for a different approach to trial deliberation; for example, four wished to have discussions over a longer duration to reinforce key messages and encourage parents to

listen objectively; two wished to communicate a more holistic "big picture" understanding of trials; and two wished for more "relaxed" conversations with potential trial participants about trial intent.

Clinician Perspective: Information Framing

When clinicians described discussing clinical trials with potential participants, they reported using a varied mix of optimistic, future-oriented statements about potential for a new DMD treatment; realistic statements about the goals of the trial; optimistic statements about the possible benefits of the clinical trial; descriptions of risks and side effects; and attempts to manage parent's expectations (see Table II). Most described a personal need to offer their patients "something more" and to give families more cause for optimism through access to clinical trials.

Table II: Clinicians' descriptions of communicating about the trial's potential

"I try to give [parents] permission to be the most hopeful of all the treatment team because I think that is the parent's right. But I think that most of the parents from time to time manifest or talk about things in an unrealistically hopeful manner, who would just say, "Come on, Doc, this is going to be the cure and my child's going to be okay, right?" On the rare occasion where they won't come out with that themselves, then I try to take a deep breath and say, "Let's talk about what the realistic options and possibilities and the fact that we won't really know for any one individual what the outcome would be...even if the statistics look good, individuals do differently." 200
"We wouldn't do it if we didn't think [the drug] had a good chance of working, but that we don't know if [the trial] will succeed, and there might be side effects that are not favorable." 203
"I have a couple phrases that I try to routinely use to make sure that I emphasize to the parents that while I'm enthusiastic about the prospect of this particular drug, that it's important that they recognize that there's no proof that this drug works in humans. It might cause some increase in dystrophin, but there's no evidence yet that that's going to result in a clinical benefit….hopefully it's a trusting situation and I know that my opinion carries a lot of weight." 205
"….And pointing out that the goal is not to cure the children, but hopefully make the lifespan into a child with Becker muscular dystrophy, rather than Duchenne. And then I take it one step further saying maybe in another ten years there'll be another breakthrough that will even enhance this medication and the children will even do better. But then I quickly add that's my fantasy and maybe my fantasy will be real, it might not be real. But at least if this medication does work, we're going to make a significant [improvement], will increase the longevity and hopefully the quality of life….And I say, there's good theories as to why this might benefit your child, but the reason we do clinical trials is because we just don't know. So I try to be very, very cautious and maybe be less than enthusiastic about how this is going to help their child. I emphasize that this is a clinical trial. This is research. It's exciting that their children are involved in the clinical trial, but no guarantees about helping the children at all. But it's better than not doing something." 207

Part 3: Informing clinical trial processes and informed consent using a community-based participatory research approach

DISCUSSION

Extending the findings of the pilot study,[6] in a range of DMD trials we found that the majority of the parents perceived themselves to have made a good and informed choice about their child's trial participation after undertaking a benefit/risk assessment. Informed choice results from having sufficient understanding of relevant information and choosing a course of action consistent with one's values and beliefs.[11] However, parents' deliberation process appeared to be complicated by strong pressures due to the progressive and ultimately fatal DMD course. This is consistent with prior research reflecting the influence of child's illness severity and availability of treatment options on parents' treatment decisions.[12]

Parents described determinations to enrol their children that simultaneously offered them essential psychological benefits and some possibility for disease benefit. Altruism was also a common, but not a strong or independent, motivator. Few parents described considering the possibility of trial failure or loss of access to the drug during their deliberation process.

Clinicians described having more influence on parental deliberations than was attributed by the parents. They felt a strong sense of responsibility to help parents make informed decisions while simultaneously allowing them to maintain hope for individual benefit. The ways that clinicians described framing their discussions with families reflects their attempts to achieve this delicate balance, while managing their own need to "offer something more" to their patients and families.

Parents and clinicians had criticisms about regulatory and industry barriers. Parents expressed a strong desire for more permissive inclusion criteria and policies that speed up the drug development timeline. Many displayed risk tolerance in the face of a progressive disorder, a finding that has been demonstrated in DMD caregivers.[13] Parents and clinicians requested less complexity in the informed consent documents and increased flexibility and an extended timeline for the informed consent process.

The primary limitation of the study is that it includes retrospective questioning. We asked parents to think back to their decision-making process. The timing of the deliberation and informed consent varied; for some parents that process occurred relatively close to the date of the interview, while for others it occurred several years in the past. Once a determination to participate is made, it is possible that parents re-frame their perceptions to be consistent with their decision.[14] The potential for retrospective bias may be especially relevant given the high emotion associated with many of our interview topics. Parents interviewed came from a group of early acceptors of clinical trial participation for their children, and their experiences and perceptions may differ from other parents of children with DMD.

CONCLUSION

Though parent participants demonstrated a good overall understanding of clinical trials, our interviews identified potential trial benefits as strong deliberative influences that were not moderated by reasonable expectations for trial success. When constructing their decision determination based on relevant information, parents most valued the chance for benefit to their child and their belief in the possibility of a different future. While this may represent what has been termed “therapeutic error,”[14] parents did not display therapeutic misconception in that they presented an understanding of the overarching intent of clinical trials.

Clinicians, sponsors, and advocacy organizations should aim to facilitate a more nuanced weighing of potential benefits and negative outcomes during trial deliberation, for example through engaging in anticipatory guidance (“what if?” scenarios) about potential negative trial outcomes. Though parents’ optimistic perceptions make such discussions difficult, well-crafted anticipatory guidance may allow parents to “try on” outcomes with the benefit of time for reflection and guidance from professionals and peers. These discussions may also aid clinicians who, through their efforts to allow families to maintain hope, may inadvertently give implicit permission for parents to hold overly optimistic motivations as primary to their deliberative process. This may facilitate informed choices that maintain psychological benefits to the parents while providing some protection against decisional regret if the child does not benefit, the trial fails, and/or the child loses access to the drug under trial.

This research reinforced an additional challenge to developing interventions. Similar to the pilot study,[6] parents reported participation determination well before the IC process and with only moderate levels of influence from clinicians. This was a barrier to clinicians, who felt it was their obligation to help families make informed decisions, and yet were frustrated with parents who "wouldn't listen" at the time of IC. Though clinicians expressed a laudable desire to have more time and flexibility to support trial deliberation, our study suggests that approaches outside the clinical setting should also be implemented. Consistent with the CBPR approach of this study, we recommend efforts to build collaborative partnerships in developing and implementing interventions that take into account the powerful influences of cross-family communication, advocacy organizations, clinicians, researchers and sponsors.

Finally, this study highlights the need for regulators and industry to appreciate the special challenges and pressures that arise in progressive pediatric disorders, where doing nothing was equated with doing harm. Our results provide support for requests that sponsors, institutional review boards, and regulatory bodies display more flexibility, permit less restrictive inclusion criteria, encourage adaptive trial design, and speed access to potential therapeutics for rare disorders.[15-17] These efforts could permit patients and families to have a wider range of decisions instead of a perceived "one-time" opportunity with potentially life-or-death implications, and may address aspects of the informed consent process that are perceived to be "broken".[18] Our study suggests a powerful opportunity for families and clinician investigators to advocate together for feasible but progressive changes to trial design and regulatory practices, based on their shared motivations for increased trial access and improved trial experiences.

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