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"Watching time tick by…": Decision making for Duchenne muscular dystrophy trials

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Abstract

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

Methods—Data from semi-structured interviews conducted with clinicians and parents in U.S. or Canada were assessed using thematic analysis.

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Results—Eleven clinicians involved in ten trials and fifteen parents involved in six trials were interviewed. Parents described benefit-risk assessments using information from advocacy, peers, professionals, and sponsors. Strong influence was attributed to the progressive nature of DMD. Most expected direct benefit. Few considered the possibility of trial failure. Most made decisions to participate before the informed consent (IC) process, but none-the-less perceived 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 IC while maintaining hope. Both clinicians and parents reported criticisms about the IC process and regulatory barriers.

Conclusions—The majority of parents described undertaking benefit-risk assessments that led to informed choices that offered psychological and potential disease benefits. Parents' high expectations influenced their decisions while also reflecting optimism. Clinicians felt challenged in balancing parents' expectations and likely outcomes. Prognosis-related pressures coupled with decision making prior to IC suggest an obligation to ensure educational materials are understandable and accurate, and to consider an expanded notion of IC timeframes. Anticipatory guidance about potential trial failure might facilitate parents' deliberations while aiding clinicians in moderating overly-optimistic motivations. Regulators and industry should appreciate special challenges in progressive disorders, where doing nothing was equated with doing harm.

Search Terms

Duchenne muscular dystrophy; clinical trial; consent; proxy decision making

Introduction

Obtaining informed consent for clinical research demonstrates respect for autonomy. To enrich the informed consent process, 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 make choices on behalf of minor children who are not considered legally competent, and yet 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 strive to facilitate informed parental decision making in the specific context of pediatric clinical trials.

Informed consent is conceptualized as an ongoing process [3] that reflects the dynamic nature of decision making. Elwyn and Miron-Shatz (2009) describe decision making as pre-decision deliberation followed by the act of making the determination. [4] 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. Determination is coming to an intention to enact the decision. [4]

The deliberation process for parents consenting to their child's participation in clinical research may be represented by weighing perceived benefits against risks. [5] For most parents, a primary motivating factor for enrolling their child in a clinical trial is the chance for individual benefit to the child [6–8]. Parents of children with a life-threatening disorder

describe more difficulty declining trial participation versus parents of children in stable health [6, 8]. Other perceived benefits may include treatments at no cost; access to the newest treatment options; increased hopefulness; the ability to help others; and increased knowledge. [4, 8–10] Perceived harms included randomization, time demands, and general inconveniences. [10] Many parents have an insufficient understanding of the distinction between the child's treatment options and options for clinical trial participation, as well as incomplete understanding of randomization [8, 9].

A pilot study of parents whose children participated in 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. [11] DMD is a rare neuromuscular disorder that causes progressive muscle weakness and death typically in the late 20s. [12,13] There are no Food and Drug Administration approved therapies, but many potential therapeutic approaches are in clinical trial. [14] 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.

Materials and Methods

This retrospective, explorative qualitative study was led by a Duchenne advocacy organization, Parent Project Muscular Dystrophy (PPMD). It 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. [15] The Research Advisory Group comprised 10 individuals: adults with Duchenne, parents of children with Duchenne, a clinician researcher, a translational researcher, a bioethicist, two clinician social scientists, and an expert in CBPR. Over a greater than two-year period, advisors led development of the semi-structured interview guide, informed thematic interpretation, deliberated on study implications, and most contributed here as authors. To achieve these goals advisors met twice in person and communicated regularly through conference calls and email.

The parent interview guide included questions on how the participant learned about the trial, the decision making process, their trial expectations and hopes, and their experience with benefits and side effects/burden. Expectations and hopes were differentiated as what the participant thought would happen and what the participant hoped might happen during the trial, respectively. Trial expectations and hopes were further explored by asking about the origins, potential threats to hopes, and changes to expectations and hopes over time.

Clinician participants were asked to describe their motivations for being involved in clinical trials, their perceptions about why people choose to participate in trials, their own expectations and hopes for the drug(s) under trial, and their communications about clinical trials with patients and potential participants, before and during the informed consent process. Two authors (Peay and Scharff) conducted the semi-structured, one-on-one telephone interviews with clinicians and parents between June and October, 2012.

Interviews were recorded and transcribed for analysis. 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 [11] that was focused on one clinical trial were excluded so that the current study could extend our understanding of decision making to a more heterogeneous study population. 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; 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 trial experiences; data on their trial experiences are not described here.

Qualitative content analysis involved data coding and analyses conducted within group and cross-group, with the groups comprising parents and clinicians. Two investigators (HS and HLP) developed the research codebook and used NVivo 9 QSR software to code responses. The coding scheme evolved through the systematic, line-by-line analysis of each transcript in an interactive, dynamic process. [16] The initial inter-coder agreement was 94% and all discrepancies in the coding were successfully reconciled. Emerging themes and representative, de-identified coded passages were explored and categorized by the Research Advisory Group into a final characterization of parents' and clinicians' perspectives and experiences. 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. Limited participant-level information was collected and is provided here, to protect privacy due to the extremely small population from which participants were drawn.

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 or was currently receiving placebo. All of the children had participated in only one therapeutic clinical trial. 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. Though some parent participants made decisions to participate in the trials several

years before the interviews, all participants described clear recall of the decision making process.

Obtaining information about the trial—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 reported positive perceptions of their interactions with the clinical research team while they were obtaining trial information. Eight 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.

> "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. It just makes the whole situation a lot better."

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 that 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.

> "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

> "I was desperate. Just let me get in any trial, some trial, any trial, you know?" Parent 102

> "I feel like this is almost our last chance because he's about to stop walking…I want to have one shot at getting him in something that might help before it's too late." Parent 113

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.

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 benefits, risks, and side effects.

Expectations and hopes for benefits: 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.

> "My expectations would be to keep <child's name> walking longer than the age of--I'll give a goal of, you know, 15." Parent 108

> "I totally understood that this was not a cure. It was not going to stop this disorder, but the impression was that he would not get any worse. And at worst, he would be stabilized and prolong the odds." Parent 111

All participants described optimistic hopes for a better outcome for their child, as well as hopes for a successful trial outcome. All but one of the parents' hopes of the CT were notably different than their expectations. Parents' hopes more often reflected future-oriented perceptions related to:

- optimistic outcomes for their children;
- a successful trial outcome;
- increased community optimism about clinical research in general; and
- long-term community benefit.

Few parents maintained hope for a curative treatment from the trial. The eleven parents who discussed "cures" during the interview identified a cure as something they used to hope for but no longer, and/or something that was not a realistic hope.

Altruism and responsibility: Though most participants reported altruistic influences on their decision making and a feeling of responsibility to participate, few described these as highly influential motivators in their assessment of potential trial benefits. Instead, altruistic outcomes were commonly described as an anticipated, important ancillary benefit of trial participation.

> "We made [son] aware that there were potential risks, but we also made sure we strongly emphasized the potential benefits to him and the fact that he'd be having an impact beyond the Duchenne community. He was being [given] an opportunity to make a difference for a lot of people….And I know that if the study doesn't

work out, it still will have benefit because there will be data that will come out of it that will inform the next." Parent 101

Perceptions of risk and burden: 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.

"You know, they are studies, they are experiments for trials. And they might end for no reason. And I still struggle with how I would accept that, but I think you need to keep that in the back of your mind, too, that you might not get the outcome that you want." Parent 101

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. The lack of treatment options and the known, progressive trajectory of DMD was commonly referenced by parents and led nine of them to a determination that action was better than inaction when faced with a progressive disorder.

"I guess the only factor is that we know what will happen if we don't put our son on any kind drugs or medication, that this is a terminal illness, so we're pretty much willing to try almost anything as long as it's not, dangerous to him." Parent 104

> "And my husband and I just decided to give it a shot. We didn't really feel like we had anything to lose. [Son's] life expectancy is only twenty, twenty-five, when we might as well give it a whirl and see what happens." Parent 110

All parents reported psychosocial benefits to their determination that included increased optimism and a feeling of empowerment to impact the progressive disease course.

> "I know that's just strictly something that's just in your head, but it feels good to be doing something, even though it may not be that magic pill, it makes it easier to cope when you feel like there's something you can do." 100

> "It's doing what we can do to battle the disease, and being involved in a clinical trial or a study is something that we were capable of doing." 117

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 either case 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 the sponsor's proprietary information about the drug, access to which may help facilitate more 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.

Discussion

Extending the findings of the pilot study, [11] 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. [17] 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. [8, 9, 18]

Parents described determinations to enroll their children that simultaneously offered them essential psychological benefits and some possibility for disease benefit. Similar to other studies of life-threatening pediatric disorders, [8] altruism was also a common, but not a strong or independent, motivator. Few parents considered the possibility of trial failure or loss of access to the drug.

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. [19] 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 was retrospective in that 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. [20] 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.

Conclusions

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 some elements of what has been termed “therapeutic error,” [20] parents did not display therapeutic misconception as they presented an understanding of the overarching intent of clinical trials.

This research reinforced an additional challenge to supporting informed choices. Similar to the pilot study, [11] parents reported making a determination to enroll their child 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.

Currently, the informed consent process is framed as researcher/participant communication that extends beyond the signing of the informed consent document to continued engagement during the course of the trial. [3] Clinicians in our study expressed a laudable desire to have more time and flexibility to support trial deliberation. Our results, however, suggest the need to re-imagine the informed consent process to take into account “pre-consent” influences. Further, the Duchenne stakeholder community has an obligation to ensure that publically available materials describing clinical trials are accurate and understandable since engaging with such materials constitutes an informal extension of the informed consent process. Consistent with the CBPR approach of this study, we recommend collaborative partnerships

in developing and implementing an expanded set of educational and decision support tools that benefit from the powerful influences of cross-family communication, advocacy organizations, clinicians, researchers and sponsors.

More immediately, clinicians should aim to facilitate a 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. Decision making may be complicated by parents' optimistic trial perceptions at the time of decision making combined with challenges related to affective forecasting, which describes people's (generally poor) ability to predict their future ability to adapt to a negative outcome [21]. Well-crafted anticipatory guidance, however, may allow parents to "try on" outcomes with the benefit of time for reflection and guidance from professionals and peers. Decision tools 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. Decision aids, which are tools developed to prepare people to engage in decision making that requires weighing risks, harms, benefits, and scientific uncertainty, have the potential to improve knowledge and the realistic perception of outcomes [22]. The overarching goal of these interventions should be facilitating informed choices that maintain psychological benefits 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.

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. [23–25] 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 help address aspects of the informed consent process that are perceived to be "broken". [26] 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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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)

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