# Community-Engaged Approaches to Explore Research Priorities in Duchenne and Becker Muscular Dystrophy

**Holly Landrum Peay**

**COLOFON**

Studies presented in this thesis were supported by grant number R21NS077286 from the National Institute of Neurological Disorders and Stroke; by the Intramural Branch of the National Human Genome Research Institute; and by Parent Project Muscular Dystrophy.

Title: Community-engaged approaches to explore research priorities in Duchenne and Becker muscular dystrophy

Author: Holly Landrum Peay

Photo Cover: Justus Kuijer
Layout: Tracey Carney
Printed by: Ipskamp Drukkers, The Netherlands
ISBN: 978-0-692-41114-8

# Community-Engaged Approaches to Explore Research Priorities in Duchenne and Becker Muscular Dystrophy

**PROEFSCHRIFT**

**ter verkrijging van**

**de graad van Doctor aan de Universiteit Leiden,**

**op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,**

**volgens besluit van het College voor Promoties**

**te verdedigen op dinsdag 21 april 2015**

**klokke 11.15 uur**

**door**

**Holly Landrum Peay**

**geboren te Washington, DC, USA**

**in 1973**

Promotiecommissie

**Promotor**

Prof. dr. A. Tibben

**Co-promotor**

Dr. B. Meiser, Prince of Wales Clinical School, Sydney, Australia

**Other members**

Prof. Dr. G.J. van Ommen

Prof. Dr. J.J.G.M. Verschuuren

Prof. B. Wilfond, MD, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute, Seattle WA, USA

For people living with DBMD and all who love them

## TABLE OF CONTENTS


# Setting an advocacy agenda using community-engaged research in Duchenne/Becker muscular dystrophy

# Introduction

## CHAPTER 1.
## Setting an advocacy agenda using community-engaged research in Duchenne/Becker muscular dystrophy

### Community Engagement

Community engagement is a form of public participation that is defined as "the process of working collaboratively with groups of people affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their wellbeing."[1] It is an approach, rather than a specific method, which values and fosters collaborations among the individuals who are the focus of the program, initiative or study; the group(s) implementing the program; and others with influence such as community leaders and government agencies. Approaches can vary dramatically in the degree of community engagement, from passive involvement through information dissemination to the target community, to active partnership of community stakeholders as decision making members of the program leadership team.[2]

Underlying community engagement approaches is the concept of **empowerment through participation**. In this context, participation has been described as: "…the process that increases a community's capacity to identify and solve problems."[3] Meaningful community participation includes the generation of ideas, contributions to decision making, and a shared responsibility for the program or intervention.[4] The approach is grounded in principles of fairness, justice, and self-determination.[4] In recent decades, public participation has evolved from an adversarial approach characterized by resistance to the establishment to active solicitation of stakeholder input by public authority figures.[5]

### Community-Engaged Research

Community-engaged research (CEnR) is a collaborative research approach where researchers engage stakeholders to propose and answer questions of interest and relevance to the stakeholder community. In this thesis, we integrated the perspectives and preferences of a broad range of stakeholders into the research process, including patients, caregivers, clinicians, patient advocates, clinical researchers, and clinical trial sponsors. CEnR is often used as a

catalyst for changing policies, programs, and practices.[1] It presupposes that people affected by the research have a right to influence what research is done and how it is conducted,[6] and that "…health issues are best addressed by engaging community partners who can bring their own perspectives and understanding of community life and health issues to a project." [4] The increased relevance that comes from community engagement is expected to improve the uptake of the evidence and the likelihood that patients will achieve the health outcomes that are important to them.[7]

Without community engagement, researchers risk imposing their own concepts of the most important health or policy concerns on a disease community. This could result in research that is less relevant to the community that channels resources away from the most important challenges.[8] Even clinicians expert in managing the health care needs of a patient population are oriented toward inquiry about health or healthcare, rather than the lived experience of the patient. [7]

A challenge of public engagement is that the approach is poorly conceptualized, spanning theoretical principles to nuanced, measurable engagement efforts. [5] To improve conceptualization, five core principles of CEnR were identified: understanding the definition and scope of community engagement in the research process; developing strong partnerships between communities and researchers that include mutual understanding of needs, capacities, and goals; facilitating equity of power, expertise, and responsibility while encouraging diverse perspectives; building capacity in all partners; and effective information dissemination based on bi-directional, transparent communication and mutual decision making about results dissemination.[9] Similarly, dimensions of community participation in biosciences include participant education, empowerment in goal setting, control over resources, the capacity to exit without penalty, opportunities to influence outcomes, measurement of outcomes, and within-group communicative capacity. [5] Strong partnerships help community members feel ownership over the program outcomes and to empower them to become agents for change.[3] An important caveat is that CEnR must not reduce scientific rigor. [7]

A review of community engagement in research partnerships identified areas in which community engagement has made a positive impact. [6] These include: influencing the research agenda; improving study design, research tools and outcome measures; and improving recruitment.[6] A second systematic review of patient and public involvement in

research found that researchers developed respect for and rapport with the community and greater insight into their areas of research. [10] There were both positive and negative impacts on the community involved in the research—increased knowledge and awareness about their condition, but also perceptions of insufficient training to contribute to research and a sense of being overburdened.[10]

Community-engaged research is most often described in the context of major public health issues and/or research in traditionally underserved communities. [6] In this thesis community engagement is employed in a different context: a rare, progressive, fatal disorder with high unmet needs (described further below). Use of community engagement is compelling in this community because there are many competing needs and limited resources. Arguably the most impactful research would be done after engaging with the community and identifying the most feasible and pressing research needs.[7] The research was intended to be translational in that it would directly inform the planning of an advocacy agenda.

To better characterize the public engagement used in this thesis, we present a model that describes a continuum of approaches to community-engaged research. The model is adapted from the United States-based ACQUIRE group's Active Community Engagement (ACE) Continuum;[2] the adaptations were based on the literature[1-9] and our experience. The model describes "stakeholder" engagement. Depending on the research objectives, stakeholders in disease communities may extend beyond patients and caregivers to also include clinicians, clinician researchers, industry groups, and advocacy organizations. The model is revisited in the concluding chapter to explore the depth and breadth of engagement in this thesis and to assess the CEnR approaches employed.

**Table 1. Community-Engaged Research Continuum (adapted from Russell et. al., 2008)**

| Characteristics of community engagement | Level 1 | Level 2 | Level 3 |
|---|---|---|---|
| **A. Inclusion of stakeholders in research program development** | • Aims and methods developed by professionals with expertise in the disease/community (i.e., specialist clinician or educator), and/or using public resources such as social media<br>• Aims/methods reviewed by and instruments informed by members of target population | • Aims and methods are researcher developed and modified based on input from one or small number of patients/caregivers<br>• Members of target population have moderate input into instrument choice or development | • Committee of stakeholders including patients/caregivers collaborate with research team to develop study aims and methods<br>• Members of target population have significant input into instrument choice or development |
| **B. Inclusion of stakeholders in decision making** | • One time, short-term input solicited from influential community leaders before or during study | • Community leaders and/or patient representatives advise research team at pre-identified time points before or during study | • Leadership committee comprising multiple stakeholders integrated as part of study team |
| **C. Increasing stakeholders' research advisory capacity** | • Researchers provide general education to patient community about area of research | PLUS<br>• Provide specific information and/or training to stakeholders who advise the research team | PLUS<br>• Develop a collaborative research leadership team where each members' expertise is equally valued and all learn together |
| **D. Disseminating study information** | • Patient-oriented recruitment materials describing aims, inclusion and exclusion criteria distributed through community forums<br>• Study results available in professional version | PLUS<br>• Introductory study information provided in lay terms, independent of recruitment efforts<br>• Study updates in lay language<br>• Lay summary of results actively disseminated to the community | PLUS<br>• Patients/caregivers actively involved in planning the information dissemination<br>• Patients/caregivers involved in developing meaningful, understandable lay summaries |
| **E. Developing accountable policy, service, and/or intervention recommendations based on outcomes of research program** | • Recommendations are determined by professionals with expertise in the disorder/community | • Recommendations are developed by research team and modified based on input from one or a small number of patients/caregivers | • Consensus recommendations are determined after community engagement; and/or through input of collaborative research leadership team |

**Duchenne and Becker Muscular Dystrophy**

Duchenne and Becker muscular dystrophy (DBMD) are rare X-linked neuromuscular disorders that occur primarily in males. The progressive muscle wasting that is the hallmark of the conditions is caused by mutations that alter production of the dystrophin protein.[11] Of the two conditions, Duchenne muscular dystrophy (DMD) is more severe and more common, with an incidence between 1:3500 and 1:6200.[12] Symptoms may appear as early as infancy and diagnosis usually occurs around age 5.[13,14] The phenotype includes progressive muscle weakness and death occurs typically in the late 20s.[13] Becker muscular dystrophy (BMD) is about a third as frequent and is more heterogeneous, ranging from a course similar to Duchenne to much milder presentations with later onset. [12] Several studies have shown high caregiving demand, burden, and stress,[15-19] and lower psychosocial and health-related quality of life[20-21] in caregivers of children with DBMD. Managing Duchenne places serious financial burden on the family.[22]

The first multi-system care guidelines for DBMD were published in 2009.[23] The standard-of-care treatment for DBMD includes the off-label use of corticosteroids, which stabilize muscle strength, delay loss of ambulation, and improve cardiopulmonary function.[23-24] There are no U.S. Food and Drug Administration (FDA) approved treatments for DBMD. In 2014 the European Medicines Agency (EMA) granted conditional approval for a drug that targets approximately 13% of patients with Duchenne.[25] Several other potential therapies are under clinical trial[26] or have recently completed clinical trials.[27] These potential treatments represent a new opportunity to intervene in a fatal disorder.

The DBMD field is at a time of tremendous advancement with robust pre-clinical research and a wide range of targets that span numerous primary and secondary pathways (for examples and a lay summary,
see http://www.parentprojectmd.org/site/PageServer?pagename=Advance_pipeline). These advancements have led to increased optimism among families, clinicians, and the advocacy community. However, most patients do not have access to novel, potentially disease-modifying therapies because participation in clinical trial is not available to them. The large majority of families have thus seen only modest changes in the management of their children with DBMD—though it is important to note that those improvements in care have led to advances in lifespan.[12,24] Families with access to clinical trials have to make difficult decisions about whether to enroll their child in a clinical trial, and if so, which trial to choose. Given the considerable

needs imposed by both the disorder and this time of growth in knowledge and opportunities, DBMD provides an appealing model for conducting community engagement to help ensure that research is focused on timely and pressing needs.

**Aims and Community-Engaged Approaches of the Thesis Studies**

The research studies included in this thesis were developed to inform the priorities and agenda of a DBMD advocacy organization called Parent Project Muscular Dystrophy (PPMD). The studies represent a range of research aims, methodologies, and levels of community engagement. Prior to each study, community engagement identified areas of need; the four distinct areas of significant need are introduced below and described in each subsequent chapter of the thesis.

***Informing interventions for mother caregivers using a stakeholder advisor approach: The Mothers' Wellbeing Study (Chapter 2)***

The impetus for the first study came from years of anecdotal reports to the advocacy organization about mothers' unmet caregiving and support needs. A small body of published literature confirms the impact of caring for children with Duchenne or Becker muscular dystrophy on caregivers. However, mothers' anecdotal communications highlighted important gaps in the literature—as well as a gap in understanding and addressing their needs, they spoke to understanding areas of strength and benefits conferred by the caregiving experience, and undertaking efforts to enhance their adaptation to caregiving for a child with DBMD.

Therefore, the goal of the study was to inform PPMD's ongoing and future efforts to improve wellbeing in mothers of individuals with DBMD. Chapter 2 presents cross-sectional data on mothers' unmet support needs and longitudinal data from the same sample on predictors of Duchenne-specific adaptation. In this CEnR approach we involved key stakeholders as advisors in the development of the longitudinal survey study. These advisors guided study objectives, aims, and methods, and helped maintain a focus on obtaining results that might lead to meaningful interventions. Advisors and parent pilot testers reviewed validated measures and informed the development of novel items on mothers' needs and strengths. The advisors and PPMD staff also recommended plans for dissemination of study findings.

***Influencing regulatory decision making using a collaborative, community-led approach: Duchenne Treatment Preferences Study (Chapters 3-5)***

The second study was developed to answer specific policy-related questions of immediate relevance to the DBMD population. As clinical trials in DBMD have progressed, questions emerged from trial sponsors and regulators about parents' and patients' treatment preference and risk tolerance. Historically, most patient and caregiver feedback is provided to regulators through testimonials. This approach has many limitations; the most significant is that those who provide testimonials may not represent the views of the entire patient population.[28,29] Thus, regulators are being asked to incorporate additional patient and caregiver input to include the views of larger groups of stakeholders,[30] and draft FDA Guidance indicated a willingness to include quantification of treatment preferences and risk tolerance in the regulatory process.[31] An overarching objective of the program was to develop a replicable model for advocacy directed at informing regulators' benefit-risk assessments.

This research program was intended to engage parents of individuals with DMD about both the DMD disease impact and their treatment preferences and risk tolerance. Three manuscripts have emerged from this study and are included in this thesis. We explored one aspect of disease impact, parental DMD-related worries, by using Best-Worst Scaling (BWS) Case 1 (Chapter 5). BWS Case 1 is used to assess participants' relative preferences for a series of related items that could otherwise be evaluated using a rating or ranking scale.[32] However, advantages of BSW Case 1 to rating scales have been demonstrated.[32] During the worries tasks, parent participants were presented with 16 sequential sets of worry items. For each task participants identified the items that were most and least worrying over the past 7 days.

The treatment preferences task described in chapters 3 and 4 used a more complex form of BWS, called BWS Case 2, as well as simple conjoint analysis. Both BWS Case 2 and conjoint analysis involve participants stating their preferences about treatment profiles that are presented to them.[32] The treatment profiles typically include different levels of treatment benefit and levels of risks, harms and/or burden. For the BWS Case 2 tasks, participants were presented with 18 simulated treatment profiles and asked to identify the best and worst aspects of each. Every treatment profile was followed by a simple conjoint task where participants indicated acceptance or rejection of the treatment, if it were available. The article under Chapter

3 reports the results of the BWS case 2 analysis, while Chapter 4 describes a comparison of the BWS and conjoint approaches.

The development and implementation of this study included rounds of community education about the objectives of the study and the study implications. It was led by PPMD with considerable organization investment. The process included extensive reporting back to stakeholders and was described and received as a community project. Study decision making rested with a small study team comprising the researchers, the President of PPMD, and several other advocacy organization staff members and volunteers with a range of backgrounds. Stakeholder advisors including families, clinician investigators, and industry professionals, all of whom had extensive input into the development of the items in the treatment preferences task. Items for the Duchenne worries task were developed by five parent volunteers.

***Informing clinical trial processes and informed consent procedures using a community-based participatory research approach: Clinical Trial Expectation and Decision Making Studies (Chapters 6-8)***

The third thesis topic assesses the implications of a relatively new phenomenon in DBMD—access to clinical trials. The research under this topic included two separate studies that explored the experiences and perceptions of parents whose children were enrolled in Duchenne clinical trials. The first was a pilot study to understand positive and negative outcomes of one trial sponsor's community engagement in trial development. An article describing that study is included as Chapter 6. The second was a community-based participatory research study with a focus on trial decision making in a range of DMD clinical trials. Two manuscripts from the second study are included as Chapters 7 and 8.

The pilot study was initiated with the support of PPMD and the qualitative interview themes were developed with their input, with an expectation that results would be used to influence community engagement for future clinical trials. Unexpectedly, the clinical trial failed immediately before the study was submitted for IRB review. Thus, the focus of the study shifted to parents' expectations of the trial and response to the trial failure.

The findings from the pilot study (Chapter 6) emphasized the need to extend our conceptualization and assessment of influences on clinical trial decision making and decision

making processes. Our intention to improve and nuance existing notions of therapeutic misconception, optimism, and mis-estimation (collectively called "therapeutic error"[33]) led to a project on parents' expectations, hopes, and clinical trial experiences in a broad range of DMD trials. The project used a community-based participatory research (CBPR) approach, in which advocates, clinicians, caregivers, and social science researchers identified the research agenda, design and delivery and led the research program.[4,5] The CBPR study included a qualitative phase and a subsequent survey phase (the latter is not described here). The interview study explored perceptions of parent decision makers as well as clinician investigators at trial sites. Results were intended to inform a conceptual decision making framework, recommendations to trial sponsors and advocacy organizations, and the development of a subsequent survey. Chapter 7 reports on parents' perceived benefits of trial participation, and Chapter 8 integrates study results and the CBPR team's guiding principles to support a decision making framework for clinical trial participation.

REFERENCES


1. CDC/Agency for Toxic Substances and Disease Registry (ATSDR) Committee on Community Engagement. Principles of community engagement. 1997. Atlanta. Accessed at www.cdc.gov/phppo/pce/
2. Russell N, Igras S, Kuoh H, Pavin M, Wickerstrom J. The active community engagement continuum. ACQUIRE Project Working Paper. 2008. Retrieved from http://www acquireproject org/fileadmin/user_upload/ACQUIRE/Publications/ ACE-Working-Paper-final pdf
3. Gryboski, K., et al. Working with the community for improved health. Health Bulletin 3. 2006. Washington, DC: Population Reference Bureau.
4. CTSA Community Engagement Key Function Committee Task Force on the Principles of Community Engagement. National Institutes of Health publication # 11-7782. 2. Washington, DC: US Department of Health and Human Services; 2011. Principles of Community Engagement. Available at: http://www.atsdr.cdc.gov/communityengagement/
5. Kelty C, Panofsky A. Disentangling public participation in science and biomedicine. Genome Med. 2014 Jan 31;6(1):8.
6. Staley K. Exploring Impact: Public involvement in NHS, public health and social care research. INVOLVE, 2009 Eastleigh.

7. Frank L, Basch E, Selby JV; Patient-Centered Outcomes Research Institute. The PCORI perspective on patient-centered outcomes research. JAMA. 2014 Oct 15;312(15):1513-4.
8. Labonte R, Robertson A. Delivering the goods, showing our stuff: the case for a constructivist paradigm for health promotion research and practice. Health Education Quarterly. 1996;23(4):431-447.
9. Ahmed SM, Palermo AGS. Community engagement in research: Frameworks for education and peer review. American Journal of Public Health. 2010; 100(8):1380–1387.
10. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, Suleman R. A systematic review of the impact of patient and public involvement on service users, researchers and communities. Patient. 2014;7(4):387-95.
11. Hoffmann EP, Brown RH, Kunkel LM: Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell. 1987; 51(6): 919-928.
12. Flanigan KM: Duchenne and Becker muscular dystrophies. Neurol Clin. 2014; 32(3): 671-688.
13. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K: Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002; 12(10): 926-9.
14. Centers for Disease Control and Prevention (CDC): Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years – four states, 2007. MMWR Morb Wkly Rep. 2009; 58(40):1119-1122.
15. Pangalila RF, van den Bos GA, Stam HJ, van Exel NJ, Brouwer WB, Roebroeck ME: Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. Disabil Rehabil. 2012; 34(12):988-996.
16. Kenneson A., Bobo, JK: The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. Health Soc Care Community, 2010; 18(5):520-528.
17. Boyer F, Drame M, Morrone I, Novella JL: Factors relating to carer burden for families of persons with muscular dystrophy. J Rehabil Med. 2006; 38(5):309-315.
18. Nereo NE, Fee RJ, Hinton VJ: Parental stress in mothers of boys with Duchenne muscular dystrophy. J Pediatr Psychol. 2003; 28(7):473-84.
19. Reid DT, Renwick RM: Relating familial stress to the psychosocial adjustment of adolescents with Duchenne muscular dystrophy. Int J Rehabil Res. 2001; 24(2): 83-93.
20. Daoud A, Dooley JM, Gordon KE: Depression in parents of children with Duchenne

muscular dystrophy. Pediatr Neurol. 2004; 31(1):16-19.
21. Hatzmann J, Heymans HS, Ferrer-i-Carbonell A, van Praag BM, Grootenhuis MA: Hidden consequences of success in pediatrics: parental health-related quality of life—results from the Care Project. Pediatrics. 2008; 122(5):e1030-1038.
22. Erik Landfeldt, Peter Lindgren, Christopher F. Bell, Claude Schmitt, Michela Guglieri, Volker Straub, Hanns Lochmuller, Katharine Bushby. The burden of Duchenne muscular dystrophy: An international, cross-sectional study. Neurology. 2014 Aug 5;83(6):529-536.
23. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy: part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010; 9:77–93.
24. Biggar WD, Harris VA, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscul Disord. 2006; 16:249–255.
25. European Medicine Agency News and Press Release Archive. European Medicine Agency recommends first-in-class medicine for treatment of Duchenne muscular dystrophy. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/05/news_detail_002110.jsp&mid=WC0b01ac058004d5c1
26. Aartsma-Rus A1, Van Ommen GJ, Kaplan JC. Innovating therapies for muscle diseases. Handb Clin Neurol. 2013; 113:1497-1501.
27. Santhera Pharmaceuticals. Clinical development of Catena®/Raxone® (idebenone) in Duchenne Muscular Dystrophy. Available at http://www.santhera.com/?docid=109&vid=&lang=en.
28. Hansen HP, Draborg E, Kristensen FB. Exploring qualitative research synthesis: the role of patients' perspectives in health policy design and decision making. The Patient: Patient-Centered Outcomes Research. 2011; 4(3):143-152
29. Hauber B, Fairchild AO, Johnson FR. Quantifying benefit-risk preferences for medical interventions: An overview of a growing empirical literature. Appl Health Econ Health Policy. 2013; 11:319-329.
30. Coplan P, Noel R, Levitan B, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit–risk balance of medicines. Clinical Pharmacology & Therapeutics. 2010; 89(2):312-315.
31. U.S. Food and Drug Administration (FDA). Factors to consider when making benefit-risk

determinations in medical device premarket approval and de novo classifications. FDA Guidance for Industry and Food and Drug Administration Staff. Silver Spring: Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, Food and Drug Administration; March 28, 2012.

32. Flynn TN. Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. Expert Rev Pharmacoecon Outcomes Res. 2010; 10(3):259-267.
33. Lynn A. Jansen. Mindsets, informed consent, and research. Hastings Center Report. 2014; 44:25-32.

# 2

# Mothers' unmet support needs and psychological adaptation to Duchenne/ Becker muscular dystrophy

**CHAPTER 2.**

## Mothers' unmet support needs and psychological adaptation to Duchenne/Becker muscular dystrophy

Holly L Peay, MS, Parent Project Muscular Dystrophy, Hackensack, NJ, USA; Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands
Bettina Meiser, PhD, Prince of Wales Clinical School, University of New South Wales, Sydney, Australia
Kathleen Kinnett, MSN, Parent Project Muscular Dystrophy, Hackensack, NJ, USA
Pat Furlong, Parent Project Muscular Dystrophy, Hackensack, NJ, USA
Kathryn Porter, JD, MPH, Parent Project Muscular Dystrophy, Hackensack, NJ, USA
Aad Tibben, PhD, Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands

**ABSTRACT**

Duchenne and Becker muscular dystrophy (DBMD) cause significant emotional and care-related burden on caregivers, but studies have not assessed predictors of disease-specific adaptation. Using a community-engaged approach focused on supporting mothers in positive aspects of caregiving, this study aims to assess mothers' unmet needs and identify predictors of mothers' psychological adaptation to DBMD.

Mothers of at least one living child with DBMD completed an online survey (n=205) and a two-year follow up (n=144). The surveys measured unmet needs, DBMD-related adaptation, optimism, resilience, perceptions of caregiving, and child's functional status.

The greatest unmet support needs were in managing future uncertainty and DBMD fears. Unmet needs were modestly but significantly higher for mothers of ambulatory children (M=1.43) than nonambulatory (M=1.12), p=0.02. Mothers indicated a desire for more information on respite care (40%). Increased psychological adaptation was predicted by resilience (β=.264, p=.001) and perceived positive impact ( β=.310, p<.001), controlling for mother's age (β=-.305, p<.001). Child's functional status did not predict adaptation.

Clinicians should address unmet support and respite needs. Though increased caregiver burden is anticipated with disorder progression, burden did not predict psychological adaptation. Efforts to improve wellbeing should instead focus on fostering resilience and benefit finding, especially as mothers age. Additional exploration is needed to better understand the effects of increasing mother's age and worsening child's functional status on support needs and psychological adaptation.

**INTRODUCTION**

Duchenne and Becker muscular dystrophy (DBMD) are rare, progressive, X-linked diseases of muscle wasting.[1] Duchenne muscular dystrophy is the more common and severe of the two disorders, with noticeable symptoms in early pediatric years.[2] It leads to severe progressive muscle weakness that results in increasing care needs as the child ages, and death typically in the late 20s.[3] Becker muscular dystrophy is more heterogeneous, ranging from a course similar to Duchenne to milder presentations with later onset and more slowly progressing weakness.[2]

Several cross-sectional studies have explored the impact of caring for a child with DBMD on parent/guardian caregivers. Studies have shown high caregiving demands and high perceived burden,[4-7] stress,[5,7,8] distress,[5,9] and lower health-related quality of life (QoL) in caregivers.[10]

Psychological outcomes have been found to be associated with factors such as child's illness progression, social support, and financial burden.[4,5,9,10]

However, survey and interview studies have also described components of DBMD caregiving that were perceived as beneficial, including an improved ability to appreciate life experiences and other positive coping strategies to manage the progressive disease course and chronic sorrow.[11-14] Pangalila and colleagues' (2012) cross-sectional study of parents of adults with DBMD found high subjective burden, but also high rating of care as important and rewarding.[4] Kenneson and Bobo[5] found that general life satisfaction was associated with high social support, high resiliency, and high income. While Hatzmann and colleagues assessed factors associated with health-related quality of life,[10] QoL is not specific to the caregiving experience and includes both positive and negative domains. Further, causation cannot be assessed from the existing cross-sectional studies. No longitudinal studies have been reported that are able to identify predictors of disease-specific caregiver wellbeing.

Studies of caregivers of other chronic disorder populations provide additional insight into wellbeing. While at increased risk for adjustment problems, the majority of caregivers demonstrated good adjustment and reported adaptive coping.[16] The importance of positive psychological responses to caregiving demands;[17-20] quality of family relationships and social supports;[10,18] time outside the home;[21-24] and financial resources[10, 24] have been demonstrated.

Though mothers caring for children with DBMD experience challenges to their wellbeing, unmet caregiving needs and DBMD adaptation can be explored in a positive framework of coping, optimism, and resilience. Disorder-specific adaptation is a wellbeing concept defined as a dynamic process of coming to terms with the implications of a health threat and the outcomes of that process.[25] Our choice of psychological adaptation to DBMD as a study outcome measure reflects the positive personal impact reported by caregivers and is consistent with the preferences expressed during community engagement (described below). Predictor variables were chosen based on the literature and through community engagement, and are described further under the "Measures" section.

**Aims and Hypotheses**

This study aims to: (i) assess mothers' unmet support, respite, and financial needs; (ii) determine the impact of the child's functional status on mothers' unmet support needs; and (ii) to determine

whether psychosocial adaptation to DBM two years later can be predicted by baseline child's functional status, mothers' dispositional optimism, resilience, perceptions of DBMD caregiving, and their coping self-efficacy.

It was hypothesized the child's functioning at the time of the baseline survey would be associated with mothers' unmet support needs and psychological adaptation—specifically, that worse child function (i.e., more severe illness) would be associated with more unmet needs and negative impacts on adaptation. It was also hypothesized that mothers' psychological adaptation as measured two years after the baseline survey would be associated with higher levels of dispositional optimism, resilience, perceived positive impact of DBMD, perceived control, and coping efficacy, and with lower levels of worry about care and perceived caregiver burden.

Longitudinal data collection is advantageous because it facilitates understanding of causality in assessing predictors of psychological adaptation. Such data will inform the development of interventions aimed at improving caregivers' wellbeing, by identifying when interventions may be most necessary and which caregivers are most likely to develop adverse psychological outcomes so that interventions can be targeted more precisely.

## MATERIALS AND METHODS

### Approach

This study used a community-engaged research approach, in which advocates, clinicians, caregivers, and social science researchers identified the research agenda, design and delivery.[26,27] Most notably, the focus of the project is responsive to a community-identified need to engage in needs assessment while appreciating and exploring positive perceptions and outcomes experienced by caregivers. The long-term objective is to develop interventions focused on meeting needs and improving adaptation rather than solely target negative impact on caregivers.

This longitudinal survey study was determined to be exempt by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

### Participants

Participants were biological mothers of at least one living child with Duchenne or Becker

muscular dystrophy, who lived in the United States, were 18 years of age or older, and able to answer questionnaires in English. The online questionnaire was implemented using SurveyMonkey software. Participants completed the baseline survey between November 2011 and October 2012, followed by a follow up survey that was distributed two years later.

**Recruitment strategy**

Recruitment was conducted through online and e-mailed advertisements and social media postings through the Duchenne Connect Registry (www.duchenneconnect.org) and Parent Project Muscular Dystrophy, and continued through snowball recruitment; and through face-to-face invitations and advertisements distributed at Cincinnati Children's Hospital Medical Center neuromuscular clinic. The total number of participants invited to the study is impossible to calculate given the variety of recruitment approaches, the use of social media and snowball recruiting, and overlap among the recruitment populations.

**Procedure**

Eligible mothers provided their contact information and each participant was asked to complete a baseline questionnaire. With the exception of two participants who requested mailed paper copies, the participants responded to surveys online using unique survey links for each participant. The unique link to a follow-up survey was sent by email at about 24 months after the baseline survey.

**Measures**

*Demographic/Disease Characteristics*: Participants' age, ethnicity, education, marital status, income, employment status, state of residence and mother's carrier status were assessed. Additional items related to the child included: diagnosis (Duchenne, Becker, or intermediary phenotype), age, age at diagnosis, and functional status. The latter was measured using a 7-item categorization where a higher score means worse condition. The same functional assessment item has been used in the DuchenneConnect patient registry and is an adaptation of the stages in the Duchenne care guidelines.[1]

*Personal Attributes*

**Dispositional optimism** was measured with the 10-item Life Orientation Test Revised (LOT-R).[28] Dispositional optimism is associated with psychological wellbeing and physical health across a range of disease populations.[29] Cronbach's alpha in this sample was 0.87. **Resilience**

was measured using the Resilience Scale for Adults (RSA), which measures 'protective resources' that have been demonstrated to facilitate flexibility in coping.[30] Cronbach's alpha was 0.94.

*Perceptions of DBMD Caregiving*

**Perceived Caregiver Burden** was measured using the 12-item Zarit Burden Interview (ZBI).[31] A score of 17 or above may be used as cut off point to identify high burden.[31] In this sample, Cronbach's alpha was 0.89. **Perceived Personal Control** was measured using five questions about control over DBMD in general, daily symptoms, long-term course, medical care and treatment, and control by others (adapted from Lipinski and colleagues).[32] Cronbach's alpha was 0.79. **Worry about Care for Child with DBMD** was measured using three items purposively designed to assess amount, frequency, and intensity of DBMD-specific care worry (developed as suggested by McCaul and Goetz).[33] Cronbach's alpha was 0.89. **Perceived Positive Impact** was measured with one item purposively developed for the study ("How much of a positive effect does your child's condition have on your entire family?"). **Coping Self-Efficacy** was assessed with the **Coping Self-Efficacy** Scale (CSES), a 26-item measure of perceived self-efficacy for coping with challenges and threats.[34] Cronbach's alpha was 0.97.

*Mothers' Unmet Needs*

The unmet needs items were purposively designed based on the literature and through community engagement.

**Unmet Support Needs** includes eight items that assess a range of unmet needs related to coping with DBDM (see Table 2). It is modelled on a needs measure utilised in a previous study.[35] It had high internal consistency with a Cronbach's alpha coefficient of .91. **Financial Need** was measured with one item, "If I had more money I could better care for my child with DBMD" scored on a 4 point Likert-type scale. The **Respite Care Needs** items range from frequency of use, information needs, attitudes, worry, and child willingness (Table 3). Each item had 6-point Likert-type responses and a "My child is independent" option. The item "I could benefit from a break from caring for my child" reduced the internal consistency and was removed from the summed score. The Cronbach's alpha was 0.73.

*Psychological Adaptation to DBMD*

The outcome variable, mothers' **psychological adaptation** to DBMD, was measured with the 20-item psychological adaptation scale (PAS), which is designed to measure adaptation to a

chronic condition or disease risk by patients or caregivers.[36] Cronbach's alpha was 0.96.

**Statistical analyses**

Data were initially explored with descriptive statistics and graphs. Separate one-way, between-groups analyses of variances (ANOVA) with approximation for homogeneity of variance, when appropriate, were conducted to assess whether child's functional status (ambulatory, children in transition to the use of a wheelchair full-time, or non-ambulatory) was associated with differences in unmet needs. For the ANOVA analyses only, to allow sufficient sample sizes the baseline child function item was re-coded into three ambulation categories: ambulatory children, children in transition to the use of a power wheelchair full-time, and full-time users of power wheelchairs.

We examined bivariate relationships among variables measured at baseline (child's functional status, dispositional optimism, worry about care, perceived control, caregiver burden, resilience, coping efficacy, and unmet support needs) and the outcome variable measured at the two-year follow up (mothers' psychological adaptation to DBMD). To assess predictors of psychological adaptation, all predictor variables with $p<0.25$ in the bivariate analysis were entered into a multiple linear regression, then progressively eliminated until only those with p-values of $<0.05$ remained. Potential confounders (mother's age, income, carrier status) were then entered one at a time and retained in the regression if the $\beta$ associated with any of the predictor variables changed by more than 10%.

Prior to analysis, child's functional status was chosen to include in analyses rather than child's age or diagnosis. The clinical variability in the DBMD diagnostic categories[1,2] makes anticipation of natural history or stage based on age difficult. Further, given the lower prevalence of Becker muscular dystrophy, it was likely there would be an insufficient sample size for analyses in that subgroup.

## RESULTS

**Sample**

Two hundred and five mothers participated in the baseline survey, and 144 participated in the follow up survey two years later (a 30% loss rate from the baseline survey cohort). This includes

two mothers who completed the baseline survey but did not complete the 2-year follow up because their affected child died between survey points.

At the time of the baseline survey, one hundred and ninety-two (93.2%) identified as Caucasian, 11 (5.3%) as Hispanic, 6 (2.9%) as Asian, and 7 (3.4%) as “other”; respondents had the option of endorsing more than one category. The mean age of the mothers was 44.0 years (SD=8.7), with a range of 27 to 71. The majority of participants had at least a college degree (136, 67.4%) and was employed or attending school part- or full-time (145, 71.5%). The median household income was $50,000-$99,999. One hundred and seventy-seven (86.3%) were married or in a long-term committed relationship, 24 (11.7%) were divorced or separated; 3 (1.5%) had never married, and 1 (0.5%) was widowed. Ninety-six participants (46.8%) reported being DBMD carriers; 78 (38.0%) were non- carriers; and 31 (15.1%) did not know whether they were carriers.

The majority of participants had one affected child (184, 89.8%), 19 (9.3%) had two affected children, and two (1.0%) had three affected children. One hundred and seventy-four (84.9%) of the affected children had DMD, 23 (11.2%) had BMD, and eight (3.9%) had an intermediate phenotype. The mean age of the affected child was 13.8 years (SD=7.2), with a range of one year to 40 years.

Mean child functional status was 3.5 (SD= 1.8, N=205) at baseline and 3.9 (SD=1.8, N=144) at 2-year follow up, with higher numbers indicating worse function. Using baseline data, the 7-item child functional categorization was re-coded into three ambulation categories: ambulatory children (83, 40.5%), children in transition to the use of a power wheelchair full-time (48, 24.4%), and full-time users of power wheelchairs (74, 36.1%). If the participant had more than one affected child, the functional status of the oldest living child is reported.

There were no statistically-significant differences in median income, mean age, or mean child functional status between those who answered the first survey only and those who answered both the baseline survey and survey at year 2.

**Personal Attributes and Perceptions of DBMD Caregiving**

Table 1 presents means and standard deviations of mothers’ perceptions of BDMD caregiving and their personal attributes. Defining a high ZBI score as 17 or above,[31] 48.2% of the mothers

reported high burden at baseline and 52.8% of the mothers reported high burden at two-year follow up.

**Table 1 Measure/Item Means: Baseline and 2-Year Follow Up**

| | Scale/Item Range | Baseline Mean (n=205) | 2 Year Mean (n=144) |
|---|---|---|---|
| Child function | 1-7 | 3.5 (SD= 1.8) | 3.9 (SD=1.8) |
| LOT-R | 0-24 | 14.3 (SD= 4.6) | __ |
| RSA | 1-5 | 3.9 (SD= 0.5) | 3.9 (SD=0.5) |
| Zarit burden | 0-48 | 17.1 (SD= 8.6) | 17.7 (SD=8.6) |
| Control | 1-11 | 5.5 (SD= 2.1) | 4.6 (SD=2.1) |
| Worry | 3-15 | 7.3 (SD= 2.9) | ___ |
| Positive impact | 0-10 | 5.6 (SD= 2.9) | ___ |
| Coping self efficacy | 0-260 | 156.5 (SD= 51.6) | 168.4 (SD= 49.4) |
| PAS | 1-5 | 3.5 (SD=0.9) | 3.6 (SD=1.0) |
| Household income | <$50,000 to ≥$250,000 | Median $50,000 - $99,999 | Median $50,000 - $99,999 |

**Mothers' Needs**

*Unmet Support Needs*

Table 2 shows the proportion of mothers reporting unmet support needs, as measured in the baseline survey. The three most frequently endorsed needs, with more than 50% responding medium or high need, were: specific ways to deal with uncertainty about the future; specific ways to manage fears related to DBMD; and specific ways to cope with being a mother of a child with DBMD. The mean score on the unmet psychosocial needs measure was M=1.31 (SD=0.7, range 0 to 3). A modest but significant difference in mean needs scores was observed depending on the child's functional status, $F$ (2, 200) =4.0, p=0.02. Post-hoc comparisons indicated that the mean score for the ambulatory children (M=1.43, SD=0.6) was significantly higher than the mean for the non-ambulatory children (M=1.12 SD=0.8). The transition to wheelchair group (M=1.38 SD= 0.7) did not differ significantly from either the ambulatory or the non-ambulatory group.

**Table 2. Mothers' Unmet Psychosocial Needs**

| | Don't have this need | Use to have this need but not anymore | Low need | Medium need | High need |
|---|---|---|---|---|---|
| Specific ways to deal with uncertainty about my child's future | 6.4% (13) | 6.9% (14) | 25.1% (51) | 34.0% (69) | 27.6% (56) |
| Specific ways to manage my fears related to my child's DBMD | 7.4% (15) | 9.4% (19) | 28.1% (57) | 34.0% (69) | 21.2% (43) |
| Specific ways to cope with being a mother of a child with DBMD | 6.9% (14) | 17.7% (36) | 22.2% (45) | 32.0% (65) | 21.2% (43) |
| Better ways to get the support I need from others | 11.8% (24) | 8.4% (17) | 28.1% (57) | 30.0% (61) | 21.7% (44) |
| Ways of self-care that improve my sense of wellbeing and happiness | 14.8% (30) | 8.9% (18) | 24.6% (50) | 31.5% (64) | 20.2% (41) |
| Specific ways to manage my sadness related to my child's DBMD | 7.4% (15) | 18.2% (37) | 25.1% (51) | 28.1% (57) | 21.2% (43) |
| How to take time for healthy life choices (such as diet and exercise) | 12.8% (30) | 11.3% (23) | 26.6% (54) | 27.6% (56) | 21.7% (44) |
| Whether the way I feel is normal | 23.6% (48) | 16.7% (34) | 30.5% (62) | 20.2% (41) | 8.9% (18) |

*Financial Needs*

In response to the item eliciting perceived financial burden, the median was 3.0 and mean was 2.76 (SD=1.17, range 1-4) and 60.7% (122) indicated “somewhat” or “very much”. No significant differences were observed in the perceived financial burden, $F$ (2, 198) = 2.8, p=0.06, based on the child’s functional status.

*Respite Needs*

Across all of the respite items (see Table 3), approximately 30% of the participants rated their child as independent, making the question not applicable. Of the remaining participants for whom the questions were applicable, 26 (21%) agreed or strongly agreed to regularly using respite care, and 37 (27%) with having all of the information they need to find respite care. Seventy-six (57%) agreed or strongly agreed that they worried about allowing others to care for their child, and 70 (53%) that their child was willing to be cared for by someone else. On the summed score, no significant differences were observed in the respite needs, $F$ (2, 46) = .61, p=0.55, based on the child’s functional status.

**Table 3. Mothers' Respite Care Needs**

| | Strongly disagree | Disagree | Neutral | Agree | Strongly agree | N/A child is in-dependent |
|---|---|---|---|---|---|---|
| I have all the information I need on how to find respite care | 14.9% (30) | 24.8% (50) | 10.9% (22) | 11.9% (24) | 6.4% (13) | 31.2% (63) |
| I regularly use respite care | 23.8% (48) | 16.3% (33) | 7.4% (15) | 8.4% (17) | 4.5% (9) | 39.6% (80) |
| Finding respite care is more trouble than it is worth* | 8.9% (18) | 13.4% (27) | 30.2% (61) | 5.9% (12) | 4.5% (9) | 37.1% (75) |
| I am worried about allowing someone else to care for my child* | 5.4% (11) | 14.9% (30) | 8.4% (17) | 22.3% (45) | 15.3% (31) | 33.7% (68) |
| My child is willing to be cared for by someone else | 5.9% (12) | 11.9% (24) | 13.4% (27) | 21.3% (43) | 13.4% (27) | 34.2% (69) |
| I could benefit from a break from caring for my child | 2.5% (5) | 4.5% (9) | 14.9% (30) | 24.3% (49) | 22.3% (45) | 31.7% (64) |
| I don't deserve a break from caring for my child* | 34.2% (69) | 19.8% (40) | 9.9% (20) | 3.0% (6) | 1.5% (3) | 31.7% (64) |

* Items are reverse scored in calculation of summed score

**Bivariate analyses**

Bivariate analysis of predictor variables and unmet support needs (measured at baseline), and psychological adaptation (measured at two-year follow up), showed statistically-significant, positive relationships between the psychological adaptation and the predictors dispositional

optimism, resilience, perceived control, positive impact, and coping self efficacy. Higher mothers' unmet support needs were associated with lower dispositional optimism, resilience, perceived control, and coping self-efficacy; and higher perceived burden. Worse child's functional status was significantly associated with lower unmet support needs and resilience; and higher perceived caregiver burden and perceived positive impact (see Table 4).

**Table 4 Pearson Correlations Among Needs, Predictors, and Psychological Adaptation (PAS)**

| Scale/Item | Unmet support needs | PAS (2 year follow up) | Child function | Mother age |
|---|---|---|---|---|
| Unmet support needs | — | -.092 | -.162* | -.232* |
| PAS | -.092 | — | .006 | -.336** |
| Child function | -.162* | .006 | — | .494** |
| Mother age | -.232* | -.336** | .494** | — |
| Household income^ | -.167* | -.133 | -.060 | .233** |
| LOT-R | -.355** | .190* | .042 | .197** |
| RSA | -.391** | .330** | -.166* | -.002 |
| Zarit burden | .307** | -.117 | .312** | .087 |
| Control | -.210** | .229* | .042 | -.097 |
| Worry | .453** | -.084 | .091 | -.044 |
| Positive impact | -.089 | .399** | .170* | -.033 |
| Coping self efficacy | -.502** | .348** | .009 | .109 |

^ Spearman rho
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

**Multivariate analyses of psychological adaptation**

A multiple linear regression was performed to assess predictors of psychological adaptation. The final model (see Table 5) included perceived positive impact (beta = .310, p<.001) and resilience (beta = .264, p=.001) and which explained 30.5% of the variance in mothers' psychological adaptation to DBMD, after controlling for effects of participants' age and income. Worry about child's care, perceived control, coping self-efficacy and perceived caregiver burden were no longer significantly associated with psychological adjustment.

**Table 5: Predictors of Psychological Adaptation at 2 Year Follow-up (N=136)**

| *Variable* | *Beta coefficient* | *T* | *p* |
|---|---|---|---|
| Household income | -.088 | -1.169 | .245 |
| Mothers' age | -.305 | -1.169 | p<.001 |
| Perceived positive impact | .310 | 4.122 | p<.001 |
| Resilience | .264 | 3,459 | P=.001 |

Final model: $R^2$ =0.325 *F* (4, 136) = 15.889, p<.001. Adjusted $R^2$ = 0.305, R = 0.570

**DISCUSSION**

This study provides clinically-relevant data about mothers' needs, strengths, and adaptation to caregiving for a child with DBMD. The use of psychological adaptation to DBMD as our primary outcome reflected stakeholders' attitudes that caring for a child with DBMD comes with benefits, and clinical interventions should focus on addressing needs and fostering positive outcomes. Greater resilience and positive impact predicted better psychological adaptation in mothers. Resilience is a multidimensional personal attribute that may be shaped by personality traits, evolving appraisals, social support systems, and family environments, and it is likely to be responsive to interventions.[37-39] Positive impact is a representation of benefit finding—a perception that major positive changes can come from a traumatic life experience.[40]

Consistent with previously-reported studies[5,6] we found that worse functional status in the child was associated with higher perceived caregiver burden, and approximately 50% of mothers reported a high level of burden. Higher perceived burden was also associated with higher unmet support needs. Although families, clinicians, and other stakeholders might anticipate increased burden to mothers with disorder progression, this study showed that burden did not predict

psychological adaptation, suggesting that mothers manage increasing caregiving burden over time. Interventions targeted at caregiver burden might not be the most effective methods to improve mothers' psychological wellbeing.

With regard to mothers' needs, the least-met support needs were coping with challenging emotions: dealing with uncertainty about the future, and fears related to DBMD. Many clinicians may benefit from further training to address these areas. In addition, we identified a need to improve knowledge about, and use of, respite care. While research underscores the importance of social support,[4,5] access to a full complement of social support may presuppose the caregiver's ability to "get away" from caregiving responsibilities. Demonstrated benefits of respite include improving caregiver, sibling, and affected child wellbeing.[41] However, our participants reported relatively infrequent use of respite care, despite a desire for respite and a perceived willingness of the affected child to accept such care. Our respite data are complicated by almost a third of participants indicating that the questions were not applicable because their child is independent, which is unexpected. This may reflect variability in knowledge about respite and access to respite care. Clinicians should anticipate that mothers may worry about allowing their children to be cared for by someone else, and support mothers in achieving higher levels of comfort.

We report unexpected relationships among mother's age, child's disease progression, unmet support needs, and adaptation. A higher score on unmet support needs was modestly but significantly associated with less disease progression in the child, and was correlated with younger mothers' ages. Higher psychological adaptation to DBMD was predicted by younger mothers' age. However, child's functional status was not a predictor of psychological adaptation. While mothers may be able to attribute more benefit to the DBMD experience and perceive that more of their support needs are met as their children's symptoms become more advanced, their resilience may be challenged as they age. It is also possible that there is a response shift in the function measure, where mothers of children in earlier stages provide more optimistic reports of their child's functional status than mothers of children progressing to later stages of DBMD. Additional exploration is needed to better understand the effects of increasing mother's age and worsening child's functional status on support needs and psychological adaptation.

Though the study sample was broadly recruited through diverse sources, possibly increasing the representativeness of the sample, the study is limited by the opt-in nature that may have

generated participation bias. This could not be evaluated, as details on individuals who did not participate were not available. In addition, the response rate cannot be evaluated given the variety of recruitment approaches, the use of social media and snowball recruiting, and overlap among the recruitment populations.

Though there was participant loss between the baseline and the survey two years later, there were no significant differences in income, age, and child functional status among those who participated only at baseline and those who participated two years later.

Traditionally underserved minority and low SES populations were under-represented in the survey, as were non-married mothers, which may have implications for the generalizability of the findings. For example, while the data do not support an increase in financial concerns as the disease progressed, most participants indicated that they would be able to better care for their children with more money. A more representative sample may have greater financial concern. Financial concerns may become more significant in the future, once new therapeutics (many of which are anticipated to be associated with high annual cost, similar to drugs for other rare disorders)[42] are approved. The study should be repeated in a generalizable clinic-based sample to strengthen the basis for clinical recommendations.

*Clinical Implications*

Care guidelines for DMD recommend family support that includes professional assessment of caregivers and families followed by proactive psychosocial interventions to meet their needs.[1] Our results highlight the need for systematic exploration of caregivers' unmet support needs, especially those related to coping with DMD-related uncertainty and fear. Efforts to improve mothers' wellbeing should focus on interventions to foster mothers' resilience, especially as mothers age, and to enhance benefit finding through identification of positive aspects of living with DBDM on the caregiver and family. Interventions that target perceived burden may not be effective at improving long-term wellbeing. Further research should evaluate a brief needs assessment and an item measuring positive DBMD impact in clinical settings. The use of needs assessment instruments in clinical encounters is well characterized; for example, as described by Boneskvi and colleagues.[43] The single impact item offers a simple, positively-valenced assessment of finding benefit in a challenging situation, and use of the item may help identify mothers for whom psychosocial interventions may be targeted. Overall, the results of this study suggest that clinical interventions can address unmet needs while highlighting strengths and

wellbeing, rather than burden and deficit.

## CONFLICT OF INTEREST

Associate Professor Bettina Meiser receives a Career Development Award Level 2 from the NHMRC. Holly Peay, Kathleen Kinnett, Pat Furlong, Kathryn Porter, and Aad Tibben declare no potential conflict of interest.

## ACKNOWLEDGEMENTS

We are grateful to the women who participated in this study. Sheila Moeschen provided valuable input into the survey development. Hadar Scharff provided database coordination and administrative support.

REFERENCES

1. Bushby K, Finkel R, Birn'krant DJ, et al., Diagnosis and management of Duchenne muscular dystrophy: part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol* 2010; **9:** 77–93.
2. Flanigan KM: Duchenne and Becker muscular dystrophies. *Neurol Clin* 2014; **32(3):** 671-688.
3. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K: Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord* 2002; **12(10):** 926-9.
4. Pangalila RF, van den Bos GA, Stam HJ, van Exel NJ, Brouwer WB, Roebroeck ME: Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. *Disabil Rehabil* 2012; **34(12):** 988-996.
5. Kenneson A., Bobo, JK: The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. *Health Soc Care Community* 2010; **18(5):** 520-528.
6. Boyer F, Drame M, Morrone I, Novella JL: Factors relating to carer burden for families of persons with muscular dystrophy. *J Rehabil Med* 2006; **38(5):** 309-315.
7. Nereo NE, Fee RJ, Hinton VJ: Parental stress in mothers of boys with duchenne muscular dystrophy. *J Pediatr Psychol* 2003; **28(7):** 473-84.

8. Reid DT, Renwick RM: Relating familial stress to the psychosocial adjustment of adolescents with Duchenne muscular dystrophy. *Int J Rehabil Res* 2001; **24(2):** 83-93.
9. Daoud A, Dooley JM, Gordon KE: Depression in parents of children with Duchenne muscular dystrophy. *Pediatr Neurol* 2004; **31(1):** 16-19.
10. Hatzmann J, Heymans HS, Ferrer-i-Carbonell A, van Praag BM, Grootenhuis MA: Hidden consequences of success in pediatrics: parental health-related quality of life—results from the Care Project. *Pediatrics* 2008; **122(5):** e1030-1038.
11. Erby LH, Rushton C, Geller G: "My son is still walking": stages of receptivity to discussions of advance care planning among parents of sons with Duchenne muscular dystrophy. *Seminars in Pediatric Neurology* 2006; **13:** 132-140.
12. Kinnett K, Eakes GG, Cripe L, Duchenne muscular dystrophy: More adults are reaching adulthood – and facing new challenges with the disease, Advance Health Network August 8, 2010. Date of last access Dec 15, 2014. Available from: http://nurse-practitioners-and-physician-assistants.advanceweb.com/features/articles/duchenne-muscular-dystrophy.aspx
13. Webb CL: Parents' perspectives on coping with Duchenne muscular dystrophy. *Child: Care, Health & Development* 2005; **31**(4): 385–396.
14. Tomiak EM, Samson A, Miles SA, Choquette MC, Chakraborty PK, Jacob PJ: Gender-specific differences in the psychosocial adjustment of parents of a child with Duchenne muscular dystrophy (DMD). *Qualitative Research Journal* 2007; **7**(2): 2-21.
15. Samson A, Tomiak E, Dimillo J, Lavigne R, Miles S, Choquette M, Chakraborty P, Jacob P: The lived experience of hope among parents of children with Duchenne muscular dystrophy: perceiving the human beyond the illness. *Chronic Illness* 2009; **5:** 103-114.
16. Wallander JL, Varni JW: Effects of pediatric chronic physical disorders on child and family adjustment. *J. of Child Psychology and Psychiatry and Allied Disciplines* 1998; **39**: 29–46.
17. Farmer JE, Marien WE, Clark MJ, et al: Primary care supports for children with chronic health conditions: identifying and predicting unmet family needs**.** *J. Pediatr. Psychol.* 2004; **29**(5): 355-367.
18. Cohen MS: Families coping with childhood chronic illness: A research review. *Families, Systems and Health* 1999*;* **7:** 149–164.
19. Silver EJ, Westbrook LE, Stein REK: Relationship of parental psychological distress to consequences of chronic health conditions in children. *J Pediatr Psychol* 1998; **23**: 5–15.
20. Thompson JL, Gil KM, Gustafson KE et al: Stability and change in the psychological adjustment of mothers of children and adolescents with cystic fibrosis and sickle cell

disease, *Pediatr Psychol* 1994; **19**(2): 171-188.

21. Kirk S: Families' experiences of caring at home for a technology-dependent child: a review of the literature. *Child Care Health Dev* 1998; **24**:101-114.
22. Brandon P: Time away from "smelling the roses": where do mothers raising children with disabilities find the time to work? *Soc. Sci. Med*. 2007; **65**: 667-679.
23. Thyen U, Kuhlthau K, Perrin JM: Employment, child care, and mental health of mothers caring for children assisted by technology. *Pediatrics* 1999; **103**: 1235-1242.
24. Kuhlthau K, Hill S, Yucel, R, Perrin JM: Financial burden for families of children with special health care needs. *Maternal and Child Health Journal* 2005; **9:** 207-218.
25. Biesecker BB, Erby L: Adaptation to living with a genetic condition or risk: a mini-review. *Clin Genet* 2008; **74:** 401-407.
26. Staley K: Exploring impact: public involvement in NHS, public health and social care research. INVOLVE 2009. Accessed October 16, 2014. Available at: http://www.invo.org.uk/posttypepublication/exploring-impact-public-involvement-in-nhs-public-health-and-social-care-research/#.
27. Clinical and Translational Science Awards Consortium Community Engagement Key Function Committee Task Force on the Principles of Community Engagement: Principles of Community Engagement, 2nd Edition. Agency for Toxic Substances and Disease Registry, National Institutes of Health publication #11-7782. 2011. Accessed October 15, 2014. Available at: http://www.atsdr.cdc.gov/communityengagement.
28. Scheier MF, Carver CS, Bridges MW: Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem) – a reevaluation of the life orientation test. *J Pers Soc Psychol* 1994; **67:** 1063–1078.
29. Glaesmer H, Rief W, Martin A, Mewes R, Br¨ahler E, Zenger M, Hinz A. Psychometric properties and population-based norms of the Life Orientation Test Revised (LOT-R). British Journal of Health Psychology 2012; 17: 432-445.
30. Friborg O, Barlaug D, Martinussen M, Rosenvinge JH, Hjemdal O: Resilience in relation to personality and intelligence. *Int J Method Psych* 2005; **14(1):** 29-42.
31. Bédard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M: The Zarit Burden Interview: a new short version and screening version. *Gerontologist* 2001; **41:** 652-657.
32. Lipinski SE, Lipinski MJ, Biesecker LG, Biesecker BB: Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling. *Am J Med Genet C Semin Med Genet* 2006; **142C(4):** 232-240.

33. McCaul KD, Goetz PW: Worry; in National Cancer Institute: Health Behavior Constructs: Theory, Measurement & Research. Accessed October 16, 2014. Available at: http://cancercontrol.cancer.gov/brp/constructs/worry/w6.html
34. Chesney MA, Neilands TB, Chambers DB, Taylor JM, Folkman S: A validity and reliability study of the coping self-efficacy scale. *Br J Health Psychol* 2006; **11:** 421-437.
35. Thewes B, Meiser B, Tucker M, Tucker K: The unmet information and support needs of women with a family history of breast cancer: a descriptive survey. *Journal of Genetic Counseling* 2003; **12**(1) 61-76.
36. Biesecker BB, Erby LH, Woolford S *et al*: Development and validation of the Psychological Adaptation Scale (PAS): use in six studies of adaptation to a health condition or risk. *Patient Educ Couns* 2013; **93(2):** 248-254.
37. Rosenberg AR, Baker KS, Syrjala KL, Back AL, Wolfe J: Promoting resilience among parents and caregivers of children with cancer. *J Palliat Med* 2013; **16(6):** 645-652.
38. Jowkar B, Friborg O, Hjemdal O: Cross-cultural validation of the Resilience Scale for Adults (RSA) in Iran. *Scand J Psychol* 2010; **51:** 418-425.
39. Ahern NR, Kiehl EM, Sole ML, Byers J: A review of instruments measuring resilience. *Issues Comp Pediatr Nurs* 2006; **29(2):** 103-125.
40. Lechner SC: Benefit Finding; in Lopez, Shane J (ed): The Encyclopedia of Positive Psychology. Blackwell Publishing, 2009. Blackwell Reference Online. Accessed October 16, 2014. Available at: http://www.blackwellreference.com/public/book.html?id=g9781405161251_9781405161251.
41. Robertson J, Hatton C, Wells E et al: The impacts of short break provision on families with a disabled child: an international literature review. *Health Soc Care Community* 2011*;* **19**(4): 337-71.
42. Zitter M: Managing drugs for rare genetic diseases: trends and insights. *Manag Care* 2005; 14(2): 52-64.
43. Bonevski B, Sanson-Fisher R, Girgis A, et al: Evaluation of an instrument to assess the needs of patients with cancer: The Supportive Care Review Group. *Cancer* 2000; 88: 217–225.

# 3

# A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy

# A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy

Holly L. Peay, MS[1]; Ilene Hollin, MPH[2]; Ryan Fischer, BA[1]; and John F.P. Bridges, PhD[2]

*[1]Parent Project Muscular Dystrophy, Hackensack, New Jersey; and [2]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland*

## ABSTRACT

**Background:** There is growing agreement that regulators performing benefit–risk evaluations should take patients' and caregivers' preferences into consideration. The Patient-Focused Drug Development Initiative at the US Food and Drug Administration offers patients and caregivers an enhanced opportunity to contribute to regulatory processes by offering direct testimonials. This process may be advanced by providing scientific evidence regarding treatment preferences through engagement of a broad community of patients and caregivers.

**Objective:** In this article, we demonstrate a community-engaged approach to measure caregiver preferences for potential benefits and risks of emerging therapies for Duchenne muscular dystrophy (DMD).

**Methods:** An advocacy oversight team led the community-engaged study. Caregivers' treatment preferences were measured by using best–worst scaling (BWS). Six relevant and understandable attributes describing potential benefits and risks of emerging DMD therapies were identified through engagement with advocates (n = 5), clinicians (n = 9), drug developers from pharmaceutical companies and academic centers (n = 11), and other stakeholders (n = 5). The attributes, each defined across 3 levels, included muscle function, life span, knowledge about the drug, nausea, risk of bleeds, and risk of arrhythmia. Cognitive interviewing with caregivers (n = 7) was used to refine terminology and assess acceptability of the BWS instrument. The study was implemented through an online survey of DMD caregivers, who were recruited in the United States through an advocacy group and snowball sampling. Caregivers were presented with 18 treatment profiles, identified via a main-effect orthogonal experimental design, in which the dependent variable was the respondents' judgment as to the best and worst feature in each profile. Preference weights were estimated by calculating the relative number of times a feature was chosen as best and as worst, which were then used to estimate relative attribute importance.

**Results:** A total of 119 DMD caregivers completed the BWS instrument; they were predominately biological mothers (67.2%), married (89.9%), and white (91.6%). Treatment effect on muscle function was the most important among experimental attributes (28.7%), followed by risk of heart arrhythmia (22.4%) and risk of bleeding (21.2%). Having additional postapproval data was relatively the least important attribute (2.3%).

**Conclusions:** We present a model process for advocacy organizations aiming to promote patient-centered drug development. The community-engaged approach was successfully used to develop and implement a survey to measure caregiver preferences. Caregivers were willing to accept a serious risk when balanced with a noncurative treatment, even absent improvement in life span. These preferences should inform the Food and Drug Administration's benefit–risk assessment of emerging DMD therapies. This study highlights the synergistic integration of traditional advocacy methods and scientific approach to quantify benefit–risk preferences. (*Clin Ther.* 2014;36:624–637) 

**Key words:** benefit–risk assessment, caregiver, choice behavior, Duchenne muscular dystrophy, patient preferences.

*Accepted for publication April 9, 2014.*
http://dx.doi.org/10.1016/j.clinthera.2014.04.011
0149-2918/$ - see front matter

## INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, life-threatening, inherited neuromuscular disorder that occurs in male subjects with an incidence of 1.3 to 2.9 per 10,000.[1,2] Diagnosis usually occurs around age 5 years, when differences in motor function become apparent, but symptoms may appear as early as infancy.[3,4] The condition is associated with significant care-related[5,6] and financial burden.[7–9] Affected individuals have progressive muscular weakness, loss of ambulation that typically occurs in the teen years, and premature death.[3] The mean age of death is in the 20s and is commonly caused by respiratory failure or cardiac disease.[3,4]

Currently, there are no therapies approved by the US Food and Drug Administration (FDA) for DMD. The standard-of-care treatment is the off-label use of corticosteroids, which have been shown to stabilize muscle strength, delay loss of ambulation by 2 to 5 years, improve cardiopulmonary function, and enhance quality of life.[3,10–12] Several potential therapies are under clinical trial that target a variety of primary and secondary effect pathways.[13]

Similar to other conditions (including other rare diseases[14] and early-on in the HIV epidemic),[15] patients and caregivers managing DMD seek to accelerate approvals for drugs that may save lives.[16] In the context of serious, rare disorders with limited treatment options, patients and patient advocates want regulators to be more permissive.[17] Drugs under trial for DMD represent a significant opportunity for families to intervene, and in public forums, some parent advocates have demanded access to drugs, even absent conclusive data on efficacy and safety.[18] DMD provides an appealing model for assessing influences on treatment decision making for serious, progressive disorders. The natural history may lead to high-pressure decisions regarding the use of novel therapies. The pediatric onset provides additional complexity, as the majority of treatment decisions are made by parents/guardians who are also the primary caregivers. These decisions may later be re-evaluated by adolescent and adult DMD patients who could have different treatment preferences.[19]

There is growing agreement that regulatory benefit–risk evaluations should be informed by the perspectives of patients and caregivers who will ultimately make treatment decisions and bear the associated risks.[20] To that end, in 2012, the FDA was congressionally mandated to engage patients to understand the impact of disease though the Patient-Focused Drug Development Initiative.[21] Although this program offers patients and caregivers an unprecedented opportunity to contribute to the regulatory process, the program is limited in scope and approach, with initially only 20 disease areas being targeted for public comment involving direct engagement with patients and caregivers.[22] Advocates who do not represent 1 of the 20 chosen disorders are left with little guidance about how to provide input that is acceptable and useful to the FDA. Existing models for FDA engagement are largely limited to providing testimonial. Although such direct engagement is a primary strength and a mainstay of advocacy organizations' efforts to inform decision makers about their community's needs and perspectives,[23] there are limitations to focusing only on patient and caregiver testimonials, such as questions about how well those providing testimonial represent the views of the entire patient population.[20,24,25] Increasingly, decision makers are being asked to consider alternative methods to quantify treatment preferences and risk tolerance that take into account the views of large groups of stakeholders.[26] Draft FDA guidance has indicated a willingness to incorporate such evidence into the regulatory process.[27] Quantitative preference elicitation methods allow stakeholders to introduce formal evidence-based decision making into the regulatory process and have been used to explore decision making and preferences among a variety of patient populations.[20]

The purpose of the present study was to demonstrate a process by which a patient advocacy organization might develop scientific evidence on treatment preferences. We aimed to model a replicable, community-engaged approach to exploring preferences in a large sample of decision makers. Specifically, our goal was to explore caregiver preferences for emerging treatments for DMD. This study is not only informative to those seeking to understand the treatment preferences and risk tolerance of DMD caregivers, but it serves to highlight principles of patient-centered outcomes research[28] by illustrating how an advocacy organization can take leadership in generating policy-relevant evidence.

## MATERIALS AND METHODS

Parent Project Muscular Dystrophy (PPMD), an advocacy organization focused on finding a cure for

DMD, led the study. The advocacy oversight team comprising PPMD staff members (a clinician, a scientist experienced in drug development, and 2 caregivers of individuals with DMD) collaborated with the research team to design and implement the study. The oversight team made study decisions through a consensus process. Consistent with the preferences of PPMD, the authoring research team was a smaller team of PPMD staff and academic collaborators.

The teams began by defining a research question about treatment preferences based on the stated needs of the Duchenne community; they then identified the study population (caregivers of individuals with DMD) and a recruitment strategy. The teams choose a stated preference method (described under the heading "Methods") that fit the study needs. In the development of the treatment experiment (described under the heading "Identifying Attributes and Levels"), the team used a community-engaged approach involving multidisciplinary stakeholder informants. The survey was piloted by a small group of end-users (described under the heading "Survey Pilot: Cognitive Interview"), and it was modified based on their input. Preliminary and final analyses were reported to regulators, industry, and the Duchenne community in an accessible and timely manner.

## Methods

Methods to measure the preferences of patients, caregivers, and other stakeholders are now well established[29,30] and are increasingly being applied to study benefit–risk preferences.[20] Although good research practices have been created to aid in the development of stated preference applications in medicine,[31] approaches such as conjoint analysis and discrete choice experiments remain complex. They require qualitative skills to appropriately identify attributes and levels and develop supporting survey text,[32] as well as quantitative skills to design the experiment[33] and analyze results.[34]

The study used best–worst scaling (BWS) case 2, an emerging stated-preference method that can be used to scientifically assess preferences.[35] Referred to as the "profile case," BWS case 2 presents profiles one at a time to elicit preferences; Flynn et al[36] fully described the method and provide use guidance. BWS has been recognized as an approach that is easier to design and analyze than conjoint analysis and discrete choice; however, this method is relatively novel in the context of measuring benefit–risk preferences.[20] The study reported here presents a novel use of the BWS case 2.[37,38] BWS is thought to be less cognitively demanding on participants than discrete choice or conjoint experiments.[36] In addition, relevant to our aim of demonstrating a replicable community-engaged model, BWS benefits from a straightforward analytic approach, the results of which are consistent with more complex approaches[39,40] that may be unfamiliar to many researchers in the clinical domain. To guide the development, implementation, and analysis of our preference elicitation instrument, we used the standards outlined in the International Society for Pharmacoeconomics and Outcomes Research checklist for conjoint analysis[27] and specific guidance on the use of BWS.[34]

### *Identifying Attributes and Levels*

BWS case 2 experiments use attributes (representing topic areas) and levels (representing attribute variables, such as amount of or impact on the attributes); Figure 1 presents an example of a BWS case 2 task. Identification of relevant and comprehensible attributes and levels is required for a meaningful study outcome. We used a stakeholder-informed approach to identify attributes and levels that were clinically relevant, meaningful, and understandable to caregivers. The development of attributes and levels was informed by PPMD's 20 years of experience with patients and families; extensive history consulting on, reviewing, and funding clinical research; and an ongoing interview study of clinical trial experiences.[41]

PPMD identified and invited stakeholder informants to participate (October–December 2012) through an existing advocacy-facilitated industry roundtable, PPMD's grassroots family networks, PPMD's clinician database, or after self-nomination following community notification of the program launch. Stakeholder informants, including patient/disease advocates (n = 5), clinicians (n = 9), drug developers from pharmaceutical companies and academic centers (n = 11), and other stakeholders (n = 5), participated in group or individual sessions. Attributes and levels for the emerging therapies were proposed and refined through iterative rounds of stakeholder engagement. Industry informants were important to successfully identify appropriate attributes because of their ability to forecast benefits and risks of premarket drugs. The

Choose the best thing in this treatment by clicking the circle under "best" and choose the worst thing by clicking the circle under "worst." You have to choose a best thing and worst thing to move on. Remember that a computer chose the combinations to make the experiment work, and some of them seem bad. Even so, please pick the best and worst thing.

| Best | Treatment | Worst |
|---|---|---|
| ○ | Slows the progression of weakness | ○ |
| ○ | 2-year gain in expected life span | ○ |
| ○ | 1-year of postapproval drug information available | ○ |
| ○ | Causes loss of appetite | ○ |
| ○ | Increased risk of bleeding gums and increased bruising | ○ |
| ○ | Increased risk of harmless heart arrhythmia | ○ |

Figure 1. Example of best–worst scaling task.

oversight committee incorporated their informative input while protecting against potential bias.

This approach yielded >20 potential benefit, adverse effect, and risk attributes. Items were grouped under themes and refined. Several attributes were rejected by the oversight team for relevance, similarity to other items, or concerns about the ability of the target population to understand the attribute. Examples of attributes that were not chosen are the ability to participate in day-to-day family activities and risks to renal and hepatic function. The participation benefit was considered to be less concrete and treatment-associated than muscle function, and thus was not chosen. The clinical implications of renal and hepatic damage were difficult to describe in a brief and accessible format. In addition, we chose not to use quantitative risks in this survey because the average US adult has only a basic level of quantitative literacy.[42]

Through a consensus process, the advocacy oversight team ultimately selected 6 treatment attributes with 3 levels each. The attributes and associated levels were chosen to be reasonable based on drugs under trial, with the notable exception that the highest risk levels represent considerably more risk than has been associated with drugs under trial, to date. The proposed attribute list was again shared with stakeholder informants. Based on their input, the final items (effect on muscle function, life span, knowledge about the drug, nausea, risk of bleeding, and risk of heart arrhythmia) were chosen by the oversight group and study team.

The BWS experiment attributes and levels are presented in Table I. The functional benefits chosen were "stops the progression of weakness" and "slows the progression of weakness" because drugs under trial are unlikely to result in a cure or significant improvement in strength for patients with DMD. The life span attribute was presented independently of the weakness attribute because drugs that affect skeletal muscle may not improve cardiac outcomes in DMD[43] and thus may not improve longevity. Caregiver participants were prompted to separate muscle function from life span by use of this cardiac example and a sample task. Given that the quality of evidence and associated uncertainty may affect preferences, we included an attribute relating to knowledge about the drug, described as the number of years of postapproval data. Nausea represents a realistic, easily understood adverse effect that may result in increasing burden as patients lose mobility. The choice of bleeding was prompted by a Phase II DMD trial that was terminated in 2011 (unpublished data). Arrhythmia was chosen as an attribute that is salient to caregivers because it is part of the DMD natural history.[44]

### *Experimental Design*

Following good research practices, we developed the BWS case 2 experiment to accommodate the 6 attributes with 3 levels each.[31] We applied a 3^6 main-effects orthogonal design, identified from the SAS database of orthogonal arrays.[45] This array consisted of 18 full-profile combinations of the attributes and levels, the minimum such number necessary to ensure no structural relationships (ie, correlations) between the attributes.[33]

As illustrated in Figure 1, in each BWS task, caregivers were presented with one of the treatment profiles and asked to judge which aspects they thought were the best and the worst. Before completing the tasks, caregivers were presented with a detailed description of all the attributes and levels to be considered in the task

Table I. Attribute, levels, and descriptions resulting from stakeholder engagement.

| Attributes and Attribute Lvels | Additional Description/Explanation in the Survey |
|---|---|
| Effect on muscle function | "How the treatment affects muscle function" |
| i Stops the progression of weakness | "Most people who take this treatment don't get any weaker over time. |
| ii Slows the progression of weakness | "Most people who take this treatment continue to get weaker over time, but more slowly than they would without treatment." |
| iii Does not change progression of weakness | |
| Lifespan | "By this we mean how many extra years of life are expected because of the treatment." |
| i 5 year gain in expected lifespan | "5 extra years of life" |
| ii 2 year gain in expected lifespan | "2 extra years of life" |
| iii No extra gain to expected lifespan | "0 extra years, meaning that the treatment may not change the person's lifespan at all." |
| Knowledge about the drug | "Important information about treatments comes after FDA approval, from tracking people who take the treatment over time. Tracking helps us better understand benefits, risks, potential drug interactions, and how the treatment affects people of different ages and stages of progression. Imagine that everyone who takes the treatment is tracked." |
| i 2 years of post-approval drug information available | "The treatment has been on the market for 2 years and we have data from 900 people with Duchenne." |
| ii 1 year of post-approval drug information available | "The treatment has been on the market for one year and we have data from 200 people with Duchenne." |
| iii No post-approval drug information available | "The treatment has just been approved and no post-approval data is available." |
| Nausea | |
| i No increased chance of nausea | |
| ii Causes loss of appetite | "A person taking the treatment loses his/her appetite" |
| iii Causes loss of appetite with occasional vomiting | "A person taking the treatment loses his/her appetite and has occasional vomiting" |
| Risk of bleeds | "Risk of bleeding" |
| i No increased risk of bleeds | |
| ii Increased risk of bleeding gums and increased bruising | "Bleeding gums and increased bruising, without increased risk of more dangerous bleeding" |
| iii Increased risk of hemorrhagic stroke and lifelong disability | "Hemorrhagic (bleeding) stroke, which could lead to lifelong disability in memory and reasoning. People found to have this risk would have to stop taking the treatment." |
| Risk of heart arrhythmia | "Risk of heart rhythm problems" |
| i No increased risk of heart arrhythmia | |
| ii Increased risk of harmless heart arrhythmia | "Occasional, harmless heart arrhythmia" |
| iii Increased risk of dangerous heart arrhythmia and sudden death | "Dangerous arrhythmia, which could lead to surgery to put in a defibrillator and risk of sudden death. People found to have this risk would have to stop taking the treatment." |

(including warm-up questions where appropriate), detailed instructions, and an explained example task. Furthermore, we confirmed that these "treatments do not currently exist" and that we were "interested in knowing what [the caregiver] would choose if they did." As a matter of context, we informed the caregivers that "we are imagining that these are approved treatments provided by the doctor, and not treatments given during a clinical trial" and asked them to "assume that all your child's medical bills, including the costs of the treatment, are covered by health insurance." We also assured respondents that this "was not a test" and that there were "no right or wrong answers." Each task incorporated a full profile (ie, all 6 attributes were shown) consisting of a specific level for each attribute. Preferences were elicited via caregivers making a judgment as to what aspect constituted the best and then the worst of the treatment.

### *Survey Instrument*

The BWS instrument was included in a broader survey. In addition to basic demographic questions, to ensure that the study sample did not represent individuals with unusually high risk-taking personality traits, the participant section included the 6-item risk-taking measure comprising items from the Jackson Personality Inventory.[46] The previously published mean (SD) score for a physician group was 19 (4), with a range of 11 to 30. We also sought to describe caregivers' numeracy by using the 3-item short form (SNS-3) of the Subjective Numeracy Scale (SNS).[47] Poor numeracy has been associated with ability to evaluate risks and benefits of health options[48] and to negatively affect utility assessment.[49] Previous research has determined a norm mean score for the SNS of 4.03 (1.04), with a range of 1 to 6.[50] Information collected about the affected children included the number of children with DMD, age, where the children lived, a mobility item (with 11 responses ranging from independent walking outdoors to remaining in bed) that represents disease progression, insurance type (private vs government), and whether the children ever experienced a life-threatening emergency.

### *Survey Pilot: Cognitive Interviewing*

Cognitive interviews with 7 parents of individuals with DMD of varying ages and disease stages were used to assess comprehension, refine terminology, and explore the acceptability of the instrument. The investigator (H.L.P.) observed the survey experience of the interviewees by using videoconferencing. Interviewees were asked to "think aloud" as they completed the survey, and the investigator used verbal probes to explore anticipated problem areas, assess understanding of the survey elements, and evaluate willingness to trade among the attributes and levels. The instrument was then modified to the final version based on pilot test feedback, again using a consensus process involving the study team and the advisory group.

### *Participants and Recruitment*

Participants were caregivers (parents or guardians) of at least 1 living child with DMD. The caregivers lived in the United States, were at least 18 years of age, and were able to complete an online survey in English. Their affected child could be any age or at any stage of the disease. The survey was administered online by using the Qualtrics survey system (Qualtrics, LLC, Provo, Utah) from January 17, 2013, to February 21, 2013. In the study advertisements, PPMD committed to sharing the information learned from the survey back to the DMD community. Recruitment occurred with the use of newsletter notices, social media, recruitment e-mails from PPMD, the DuchenneConnect self-report registry, and through word-of-mouth recruiting. The anonymous survey was determined to be exempt by the Western Institutional Review Board (no. 1-756840-1).

### *Statistical Analysis*

In BWS, the dependent variable is the participants' judgment about the best and worst feature in each profile presented to them.[51] Although the results from a BWS can be estimated by using complicated techniques such as conditional logit[52] or hierarchical Bayes,[53] one of the benefits of the method is that it can be analyzed very simply. The simplest techniques focus on the number of times a particular level of an attribute was chosen as best and as worst when it was available in the choice task (unpublished data). A relative best-minus-worst (BW) score can be calculated by subtracting the number of times a feature was chosen as worst from the number of times it was chosen as best, then dividing by the total number of times it was available to be chosen. Early applications of this method have demonstrated a very high level of correlation between such simple techniques and more complicated regression-based techniques.[39,40] As with all techniques used to estimate ordinal, multinomial

outcomes, our scoring approach assumes equal spacing between things that were chosen as best (BW score, 1), those that were not chosen (BW score, 0), and those chosen as worst (BW score, –1).

We chose to estimate the importance weights for each level by using the relative BW score because it could be easily understood by the broadest readership (including the community of patients and caregivers that we engaged in developing this survey). In addition to the simplicity of the BW score, this approach has several advantages. First, regression-based techniques require the use of the omitted category[39] or the use of complex effects coding procedures[40] to estimate choice models. Second, by using this simple approach, we have ensured that all estimated parameters remain on the same ratio scale. This method allows comparisons to be made across the attributes, as well as identification of global best and worst attribute levels across all the attributes. Because the BW score is estimated as a mean across the sample, we also report the SEs for these means. This process allows us to conduct *t* tests to determine whether the scores were significantly different from zero. We did this for each attribute level and have reported the *P* values for each test.

Finally, we used the relative BW score for each level within each attribute to assess the overall importance of each attribute, conditioned on the levels chosen.[54] With this technique, relative attribute importance was estimated by subtracting the lowest relative BW score associated with a level of that attribute from the highest relative BW score associated with a level of that attribute. We then divided each difference by the sum of all differences across the 6 attributes and reported the result as a percentage.

## RESULTS

A total of 124 caregivers who self-identified as being a parent or guardian of an individual with DMD began the treatment experiment. Two individuals dropped out after the first treatment task; 1 dropped out after the third treatment task; 1 dropped out after the fifth treatment task; and 1 dropped out after the 15th treatment task. The remaining 119 caregivers completed the entire survey.

Table II summarizes the characteristics of the sample. Caregivers were predominantly white, married, biological mothers, and had 1 affected child. Education level ranged from high-school or General Educational Development diploma to graduate or professional degree; the median response was "4-year college degree." Annual household income ranged from "<$25,000" to ">$100,000"; the median response was "$75,000 to $100,000." Caregivers' ages ranged from 28 to 66 years (mean, 43.7 years), and the age of the affected children ranged from 2 to 38 years (mean, 12.1 years). Slightly more than one half of the children were reported as having participated in clinical research and more than one third in a clinical trial. Almost all of the affected children lived in the home of the caregiver (n = 117 [98%]). The majority of the affected children used private insurance for their medical care (n = 101 [85%]), although 34% (n = 40) endorsed that their child used a state/government program. Caregivers reported that 19% (n = 22) of their children had experienced a life-threatening emergency.

The affected children represented a range of disease progression. When these children were dichotomized into an "ambulatory" group, defined as those who could walk independently outdoors for at least short distances, and a "nonambulatory" group, defined as those who could not walk outdoors without help, 75 (64%) were parents with children in the ambulatory group and 43 (36%) were parents with children in the nonambulatory group.

The mean (SD) risk-taking score was 17 (4), with a range of 7 to 30 (higher scores indicate more risk-taking endorsement). The caregivers in this study scored significantly lower on the risk-taking score than the physician reference group[41] (mean, 19 [4]; $P < 0.005$), indicating lower risk-taking personality traits. The mean SNS-3 score was 4.90 (1.1), with a range of 2.33 to 4.87, which was higher than the reference population.[42] This result was consistent with the high educational levels reported in our study (68% with at least a college degree).

Table III presents relative BW scores, SEs, and *P* values, and Figure 2 diagrams the relative utility of each level as measured by using relative BW scores. All of the BW scores were significant at $P < 0.001$ except for "no increased chance of nausea," "no postapproval drug information available," and "no increased risk of bleeding." By a large margin, the highest utilities as measured by using relative BW scores were for "stops progression of weakness" (0.877) and "slows progression of weakness" (0.800). These scores had almost twice the utility of

Table II. Characteristics of participants and affected children (N=119)

| Characteristic | Value |
|---|---|
| Participant characteristics | |
| Mean (SD) caregiver age, y | 43.7 (7.7) |
| Mean (SD) child age, y | 21.1 (6.4) |
| Caregiver characteristics | |
| Relationship to children | |
| Biological mother | 67.2% |
| Biological father | 28.6% |
| Adoptive mother | 3.4% |
| Adoptive father | 0.8% |
| Marital status | |
| Married/long-term relationship | 89.9% |
| Divorced/separated | 9.2% |
| Widowed | 0.8% |
| Race | |
| White | 91.6% |
| Education | |
| High school/GED | 4.2% |
| Some college | 14.3% |
| Technical school | 5.0% |
| Associated degree | 7.6% |
| 4-year college degree | 42.9% |
| Graduate/professional degree | 25.2% |
| Income | |
| <$25,000 | 5.9% |
| $25,000–$50,000 | 8.4% |
| $50,000–$75,000 | 18.5% |
| $75,000–$ 100,000 | 18.5% |
| >$100,000 | 47.1% |
| Child characteristics | |
| No. of affected children | |
| 1 child | 92.4% |
| ≥2 children | 7.6% |
| Living arrangements | |
| In caregiver's home | 98.3% |
| Independent | 0.8% |
| Other | 0.8% |
| Ambulation status | |
| Ambulatory* | 63.9% |
| Nonambulatory | 36.0% |
| Research participation | |
| Clinical research | 58.0% |
| Clinical trial | 34.0% |
| Had life-threatening emergency | |
| Yes | 18.5% |
| No | 81.5% |

Note: In some cases, percents do not add to 100% because of missing values.
GED = General Educational Development diploma.
*Ability to walk independently outside for at least short distances.

the next-highest score, "5-year gain in expected life span" (0.464). The "2-year gain in expected life span" had a similar priority to the "5-year gain in expected life span" (0.408).

Caregivers attributed the highest negative BW scores to "increased risk of dangerous heart arrhythmia and sudden death" (–0.786), followed by "increased risk of hemorrhagic stroke and lifelong disability" (–0.720). This was followed by "causes loss of appetite with occasional vomiting" (–0.280). Although the 2 most serious risks had high negative scores, either (but not both) could be offset by a treatment that stopped the progression of weakness. The amount of knowledge about the drug was not given high relative BW scores at any level, with mean scores ranging from 0.056 to –0.021.

Table IV includes the relative attribute importance for the entire group of caregivers. At the attribute level, effects on muscle function accounted for the largest proportion of the variance (28.7%), followed by arrhythmia (22.4%), bleeding (21.2%), life span (17.3%), nausea (8.1%), and knowledge about the drug (2.3%).

## DISCUSSION

Although the FDA is committed to patient-centered drug development, the agency has limited resources. Representing a disease community that was not selected for the congressionally mandated community engagement program, PPMD led a study to proactively inform the FDA's benefit–risk assessments. The process we used can be a model for facilitating patient-centered drug development through an exploration of the priorities and

Table III. Best-worst results.

| Attribute description | Best | Worst | Best-worst | Relative b-w Score | S.E. | T-test | P-Value |
|---|---|---|---|---|---|---|---|
| Effect on muscle function | | | | | | | |
| Stops the progression of weakness | 628 | 2 | 626 | 877 | 0.013 | 69.441 | <0.001 |
| Slows the progression of weakness | 571 | 0 | 571 | 0.800 | 0.015 | 53.357 | <0.001 |
| Does not change progression of weakness | 68 | 125 | −57 | −0.080 | 0.019 | −4.149 | <0.001 |
| Lifespan | | | | | | | |
| 5 veargain in expected lifespan | 348 | 17 | 331 | 0.464 | 0.020 | 22.741 | <0.001 |
| 2 veargain in expected lifespan | 299 | 3 | 291 | 0.408 | 0.019 | 21.186 | <0.001 |
| No extra gain to expected lifespan | 12 | 93 | −81 | −0.113 | 0.014 | −8.269 | <0.001 |
| Knowledge about the drug | | | | | | | |
| 2 years of post-approval drug info available | 109 | 69 | 40 | 0.056 | 0.019 | 3.015 | 0.001 |
| 1 year of post-approval drug info available | 20 | 4 | 16 | 0.022 | 0.007 | 3.288 | 0.001 |
| No post-approval drug info available | 41 | 56 | −IS | −0.021 | 0.014 | −1.524 | 0.064 |
| Nausea | | | | | | | |
| No increased chance of nausea | 19 | 26 | −7 | −0.010 | 0.009 | −1.044 | 0.148 |
| Causes loss of appetite | 1 | 95 | −94 | −0.132 | 0.013 | −10.272 | <0.001 |
| Causes loss of appetite with occasional vomiting | 17 | 217 | −200 | −0.280 | 0.019 | −14.981 | < 0.001 |
| Risk of bleeds | | | | | | | |
| No increased risk of bleeds | 3 | 11 | -8 | −0.011 | 0.005 | −2.143 | 0.016 |
| Increased risk of bleedinggums and increased bruising | 0 | 190 | −190 | −0.266 | 0.017 | −16.079 | <0.001 |
| Increased risk of hemorrhagic stroke and lifelong disability | 0 | 514 | −514 | −0.720 | 0.017 | −42.807 | < 0.001 |
| Risk of heart arrhythmia | | | | | | | |
| No increased risk of heart arrhythmia | 5 | 32 | −27 | −0.038 | 0.008 | −4.498 | <0.001 |
| Increased risk of harmless heart arrhythmia | 1 | 122 | −121 | −0.169 | 0.014 | −11.943 | <0.001 |
| Increased risk of dangerous arrhythmia and sudden death | 0 | 551 | −561 | −0.786 | 0.015 | −51.131 | <0.001 |

preferences of patients, families, and other stakeholders. Although the individual stories of highly motivated advocates are powerful and influential, it is difficult to know whether these testimonials represent the perspectives of the majority of patients and families. We describe a successful community-engaged process to understand treatment preferences in a large group of decision makers supported by the use of best/worst scaling. To the best of our knowledge, this study represents the first time a patient advocacy organization has led a quantitative preferences study of this complexity, highlighting a successful advocacy/academic collaboration that integrates traditional advocacy methods, family-centered outcomes research, and a scientific approach to quantifying preferences.

Within the context of our experiment, caregivers attributed very high scores to stopping or slowing the progression of muscle weakness. Change in life span was not scored as highly. Feedback during cognitive interviewing suggested that parents associated better muscle function with higher quality of life, indicating that parents value quality more than length of life. This finding is consistent with both anecdotal reports and an interview study of parents of children involved in clinical trials,[41] in which parents expressed a preference for better quality of life for their child over a longer life span.

We found that the presence of a serious risk could be compensated for by a treatment that stops or slows progression of weakness, even absent any other benefits. The burden of DMD may be associated with parents' willingness to accept a serious risk for a noncurative treatment. The data support a limit to parents' risk tolerance, however: for the levels of benefit provided in the experiment, they would not accept a treatment with 2 serious risks.

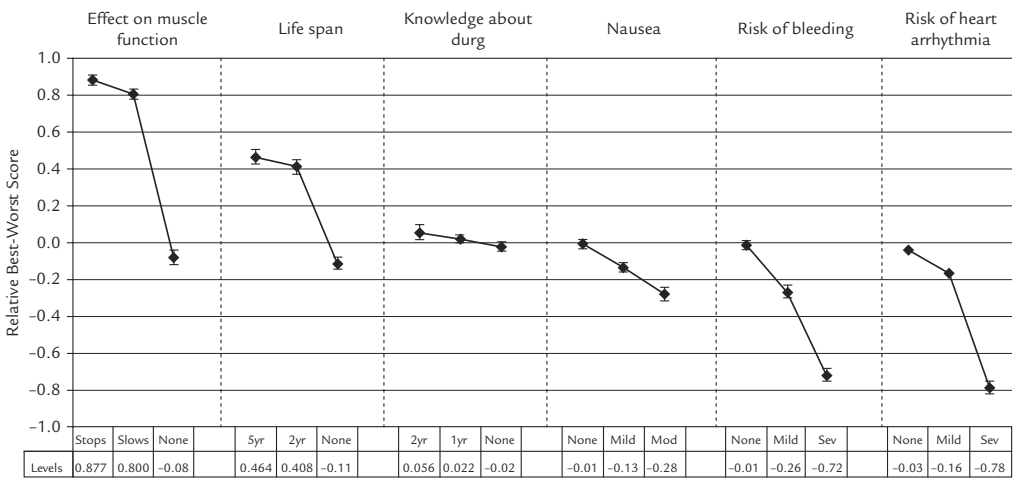



Figure 2. Relative best–worst scores for attribute levels. Mod = moderate; Sev = severe.

Our community-engaged process contributed to successful recruitment of sufficient numbers of caregivers for a complex, time-intensive survey in only 5 weeks, notwithstanding the fact that the study focuses on a rare disease. The caregivers' children represented a range of ages and disease stages, and thus our outcomes reflect the preferences of parents with children across the disease course. Although the development of an appropriate experimental design is a complex task, it is one that is well suited to be led by advocacy organizations with expert input and collaboration.

## Limitations

There are several limitations to the study. First, the study sample, although likely to be representative of caregivers whose children are enrolled in clinical trials, may not be generalizable to the broader DMD community. However, we have demonstrated that this population was not unusually high in risk-taking

Table IV. Relative attribute importance.

| Attribute | Maximum | Minimum | Difference | Percent* |
|---|---|---|---|---|
| Effect on muscle function | 0.877 | −0.080 | 0.957 | 28.7 |
| Life span | 0.464 | −0.113 | 0.577 | 17.3 |
| Knowledge about the drug | 0.056 | −0.021 | 0.077 | 2.3 |
| Nausea | −0.010 | −0.280 | 0.270 | 8.1 |
| Risk of bleeding | −0.011 | −0.720 | 0.709 | 21.2 |
| Risk of heart arrhythmia | −0.038 | −0.786 | 0.748 | 22.4 |
| Sum | | | 3.338 | 100 |

*Percent relative importance calculated as the difference between the maximum and minimum utility for each attribute divided by the sum of all such differences.

personality traits and had adequate numeracy to reduce concern about numeracy bias in survey responses. Although the recruitment of caregivers (or patients) through advocacy groups has a risk of bias, it also has real benefits over qualitative approaches. Using the model process, we plan to refine the experiments and conduct a larger study with a more representative parent group and a neuromuscular clinician group. Especially important in our next study is to elicit treatment preferences from affected teenagers and adults, anticipating that DMD patients and caregivers may not assess benefit and risk in the same way.[19]

Second, although the study used a rigorous approach to attribute identification, the simulated treatments described in the experiment may not represent the benefit and risk profile of therapies that are ultimately approved for DMD. As with all stated-preference experiments, it remains unknown whether the presence or absence of additional attributes would influence the results. On the spectrum of patient centered to clinically centered specification of attributes, we favored the former to be consistent with the goals of patient-centered outcomes research and explore attributes meaningful to our caregiver participants. In our future studies, and when more is known about the benefits and risks of treatment, we aim to incorporate more clinically centered attributes while continuing to maintain a priority on utilizing meaningful attributes.

Third, we conducted an aggregate analysis, and important structures in preference heterogeneity may have been overlooked. We have previously reported the differences in treatment preferences by stratifying data according to child's ambulation status.[55] Although there was a small but significant difference when completing such a stratification, this could have been explained by scale differences between the 2 groups. In follow-up studies, we will aim to have a larger sample size to allow for both stratification and segmentation analysis,[56] which will enable being able to adequately describe preference heterogeneity.

Fourth, we used a simple technique for estimating preferences, compared with more advanced regression techniques. As a supplemental analysis (not reported here), we reanalyzed our data by using a conditional logit. One obvious difference between the methods is that conditional logit requires using effects coding for each attribute, making each attribute have the same mean. As such, although each attribute remains on a ratio scale, the translocation of the origin inherent in effects coding implies that level importance cannot be compared across attributes. The advantage of our simple approach is that all preference weights can be estimated directly (ie, without using effects coding), and hence they all sit on the same ratio scale. We modified these results to make them comparable to the conditional logit (ie, we subtracted the attribute mean from each attribute level), and they produced nearly identical results to the conditional logit, with both methods having identical ordering (Spearman's $\rho = 1.0$) and near perfect correlation (Pearson's $\rho = 0.997$).

Finally, because BWS is a relatively new stated-preference method, there is the possibility that it may present a distorted version of preference. However, there is growing interest in the method given its simplicity compared with more traditional conjoint analysis methods, which may affect respondent efficiency (ie, do responses to choice tasks reflect respondents true preferences?). We plan to validate these results against a simple conjoint analysis that was conducted as part of this study, but more research is needed to compare BWS and conjoint analysis methods.

## Implications

The study findings are highly relevant to industry and regulators who are conducting benefit–risk assessments for potential DMD therapies. Emerging results from clinical trials suggest a slowing of motor decline, as measured by using the 6-minute talk test, and no known effect on life span.[13] Caregivers' significant and yet finite risk tolerance has regulatory implications as well; however, given the modest risk profile emerging from many DMD clinical trials, our finding of high tolerance for adverse effects and drug-related uncertainty is also relevant.

This study intended to leverage the FDA's ongoing commitment to identifying methods of systematic patient engagement and, more specifically, their commitment to the use of statistical methods exploring and comparing benefits and risks to systematically quantify patients' anecdotal reports.[57] PPMD was able to report the outcome of this study to FDA representatives in both private and public meetings. Equally important, PPMD reported the results back to the DMD community through social media, a webinar, and in-person meetings and conferences. As the FDA evaluates new drug applications for DMD therapies, they should be mindful of the value that

parent decision makers place on even moderate benefits to function, their tolerance for considerable risk, and their tolerance for uncertainty.

## ACKNOWLEDGMENTS

We appreciate the leadership and commitment of the PPMD oversight committee: Pat Furlong, Brian Denger, Sharon Hesterlee, and Kathi Kinnett. We are indebted to the stakeholder informants, parents who participated in the cognitive interviews, and caregivers who completed the survey.

Ms. Peay was responsible for community engagement, survey development, and writing and contributed to data analysis and data interpretation. Ms. Hollin was responsible for figure creation and contributed to data analysis, data interpretation, and writing. Mr. Fischer contributed to community engagement and survey development. Dr. Bridges was responsible for study design, data analysis, and data interpretation and contributed to survey development and writing.

## CONFLICTS OF INTEREST

This study was funded by Parent Project Muscular Dystrophy, which had a role in the study design; in the collection, analysis, and interpretation of data; in writing the manuscript; and in the decision to submit the manuscript for publication. Ms. Peay and Mr. Fischer are employees of PPMD, and Dr. Bridges received compensation from PPMD for this project. The authors indicated that they have no conflicts of interest regarding the content of this article.

## REFERENCES

1. Centers for Disease Control and Prevention (CDC). Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years—four states, 2007. *MMWR Morb Wkly Rep*. 2009;58:1119–1122.
2. Emery AE. Population frequencies of inherited neuromuscular diseases—a world survey. *Neuromuscul Disord*. 1991;1:19–29.
3. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9:77–93.
4. Eagle M, Baudouin SV, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord*. 2002;12:926–929.
5. Pangalila RF, van den Bos GA, Stam HJ, et al. Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. *Disabil Rehabil*. 2012;34:988–996.
6. Kenneson A, Bobo JK. The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. *Health Soc Care Community*. 2010;18:520–528.
7. Larkindale J, Yang W, Hogan PF, et al. Cost of illness for neuromuscular diseases in the US. *Muscle Nerve*. 2014; 49:431–438.
8. Ouyang L, Grosse SD, Fox MH, Bolen J. A national profile of health care and family impacts of children with muscular dystrophy and special health care needs in the United States. *J Child Neurol*. 2012;27:569–576.
9. Ouyang L, Grosse SD, Kenneson A. Health care utilization and expenditures for children and young adults with muscular dystrophy in a privately insured population. *J Child Neurol*. 2008;23:883–888.
10. Biggar WD, Harris VA, Eliasoph L, Alman B. Long-term benefits of Deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. *Neuromuscul Disord*. 2006;16:249–255.
11. Angelini C. The role of corticosteroids in muscular dystrophy: a critical appraisal. *Muscle Nerve*. 2007;36:424–435.
12. Bushby K, Muntoni F, Urtizberea A, et al. Report on the 124th eNMC International workshop. Treatment of Duchenne muscular dystrophy; defining the gold standards of management in the use of corticosteroids. *Neuro Muscul Disord*. 2004;14:526–534.
13. Govoni A, Magri F, Brajkovic S, et al. Ongoing therapeutic trials and outcome measures for Duchenne muscular dystrophy. *Cell Mol Life Sci*. 2013;70:4585–4602.
14. Milne CP. Prospects for rapid advances in the development of new medicines for special medical needs. *Clin Pharmacol Ther*. 2014;95:98–109.
15. Michaels M, Collyar D. Research advocacy in traditional research settings: questions of influence and legitimacy. In: Earp JL, French EA, Gilkey MB, eds. *Patient Advocacy for Healthcare Quality: Strategies for Achieving Patient-Centered Care*. Boston, Mass: Jones and Bartlett; 2007:445–473.
16. Parent Project Muscular Dystrophy. Benefit-risk assessments in rare disorders: The case for therapeutic development in Duchenne muscular dystrophy as the prototype for new approaches. http://www.parentprojectmd.org/BR. Accessed April 28, 2014.
17. Genetic Alliance UK. New medicines for serious conditions: weighing the risks and benefits. The verdict of a jury of patients. http://www.geneticalliance.org.uk/docs/citizens-jury-report.pdf. Accessed March 1, 2014.
18. Parent Project Muscular Dystrophy: Share Your Brave Story. http://community.parentprojectmd.org/profiles/blog/list?tag=My+BRAVE+Story. Accessed March 1, 2014.
19. McNeil DE, Davis C, Jillapalli D, et al. Duchenne muscular dystrophy: drug development and regulatory considerations. *Muscle Nerve*. 2010;41:740–745.
20. Hauber B, Fairchild AO, Johnson FR. Quantifying benefit-risk preferences for medical interventions: an overview of

a growing empirical literature. *Appl Health Econ Health Policy*. 2013;11: 319–329.

21. US Food and Drug Administration (FDA). Enhancing benefit-risk assessment in regulatory decision-making. http://www.fda.gov/forindustry/userfees/prescriptiondrugu serfee/ucm326192.htm. Accessed March 1, 2014.
22. Mullard A. Patient-focused drug development programme takes first steps. *Nat Rev Drug Discov*. 2013;12: 651–652.
23. Facey K, Boivin A, Gracia J, et al. Patients' perspectives in health technology assessment: a route to robust evidence and fair deliberation. *Int J Technol Assess Health Care*. 2010;26:334–340.
24. Hansen HP, Draborg E, Kristensen FB. Exploring qualitative research synthesis: the role of patients' perspectives in health policy design and decision making. *Patient*. 2011; 4:143–152.
25. Vogt F, Schwappach D, Bridges J. Accounting for tastes: a German perspective on the inclusion of patient preferences in health care. *Pharmacoeconomics*. 2006;24:419–423.
26. Coplan P, Noel R, Levitan B, et al. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit–risk balance of medicines. *Clin Pharmacol Ther*. 2010; 89:312–315.
27. US Food and Drug Administration (FDA). *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. FDA Guidance for Industry and Food and Drug Administration Staff*. Silver Spring, Md: Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. Food and Drug Administration. March 28, 2012.
28. Fleurence R, Selby JV, Odom-Walker K, et al. How the Patient-Centered Outcomes Research Institute is engaging patients and others in shaping its research agenda. *Health Affairs*. 2013;32:393–400.
29. Bridges J, Hauber AB, Marshall D, et al. A checklist for conjoint analysis applications in health: report of the ISPOR Conjoint Analysis Good Research Practices Taskforce. *Value Health*. 2011;14:403–413.
30. Marshall D, Bridges J, Hauber AB, et al. Conjoint analysis applications in health—how are studies being designed and reported? An update on current practice in the published literature between 2005 and 2008. *Patient*. 2010;3:249–256.
31. Bridges J, Kinter E, Schmeding A, et al. Can patients diagnosed with schizophrenia complete choice-based conjoint analysis tasks. *Patient*. 2011; 4:267–275.
32. Coast J, Flynn TN, Salisbury C, et al. Maximising responses to discrete choice experiments: a randomised trial. *Appl Health Econ Health Policy*. 2006;5:249–260.
33. Reed Johnson F, Lancsar E, Marshall D, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. *Value Health*. 2013;16: 3–13.
34. International Society for Pharmacoeconomics and Outcomes Research. ISPOR Statistical Methods for Conjoint Analysis Task Force. http://www.ispor.org/TaskForces/Analyzing_Data_Conjoint_Analysis.asp. Accessed March 1, 2014.
35. Erdem S, Rigby D, Wossink A. Using best-worst scaling to explore perceptions of relative responsibility for ensuring food safety. *Food Policy*. 2012;37:661–670.
36. Flynn TN, Louvier JJ, Peters TJ, Coast J. Best-worst scaling: what it can do for health care research and how to do it. *J Health Econ*. 2007; 26:171–189.
37. Bridges J. Stated preference methods in health care evaluation: an emerging methodological paradigm in health economics. *Appl Health Econ Health Policy*. 2003;2:213–224.
38. Flynn TN. Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10:259–267.
39. Louviere JJ, Flynn TN. Using best-worst scaling choice experiments to measure public perceptions and preferences for healthcare reform in Australia. *Patient*. 2010;3:275–283.
40. Gallego G, Bridges J, Flynn T, et al. Using best-worst scaling in horizon scanning for hepatocellular carcinoma technologies. *Int J Technol Assess Health Care*. 2012;28:339–346.
41. Peay HL, Sheffer H, Tibben A. Expectations and decision making in clinical trials for Duchenne and Becker muscular dystrophy. Abstract presented at: 18th International Congress of The World Muscle Society; October 1–5, 2013; Asilomar, Calif.
42. National Center for Education Statistics. National assessment of adult literacy (NAAL). A first look at the literacy of America's adults in the 21st century. https://nces.ed.gov/pubsearch/pubsinfo.asp?pubid=2006470. Accessed March 1, 2014.
43. Townsend D, Yasuda S, Li S, et al. Emergent dilated cardiomyopathy caused by targeted repair of dystrophic skeletal muscle. *Mol Ther*. 2008; 16:832–835.
44. Shirokova N, Niggli E. Cardiac phenotype of Duchenne muscular dystrophy: insights from cellular studies. *J Mol Cell Cardiol*. 2013;58: 217–224.
45. Kuhfeld W. Orthogonal arrays [TS-723]. Cary (NC): SAS http://support.sas.com/techsup/technote/ts723.html. Accessed March 1, 2014.
46. Pearson SD, Goldman L, Orav EJ, et al. Triage decisions for emergency department patients with chest pain: do physicians' risk attitudes make the difference? *J Gen Intern Med*. 1995;10:557–564.

47. Wallston KA, McNaughton C, Storrow A, et al. Validation of a short, 3-item version of the Subjective Numeracy Scale (SNS-3). Presented at: Health Literacy Research Conference; October 17-18, 2011; Chicago, IL.
48. Peters E, Hibbard J, Slovic P, Dieckmann N. Numeracy skill and the communication, comprehension, and use of risk-benefit information. *Health Affairs*. 2007;3:741–748.
49. Zikmund-Fisher B, Smith DM, Ubel PA, Fagerlin A. Validation of the Subjective Numeracy Scale: effects of low numeracy on comprehension of risk communications and utility elicitations. *Med Decis Making*. 2007;27:663–671.
50. Fagerlin A, Zikmund-Fisher BJ, Ubel PA, et al. Measuring numeracy without a math test: development of the Subjective Numeracy Scale. *Med Decis Making*. 2007;27:672–680.
51. Molassiotis A, Emsley R, Ashcroft D, et al. Applying best-worst scaling methodology to establish delivery preferences of a symptom supportive care intervention in patients with lung cancer. *Lung Cancer*. 2012;77:199–204.
52. McFadden D. Conditional logit analysis of qualitative choice behavior. In: Zarembka P, ed. *Frontiers in Econometrics*. New York, NY: Academic Press; 1974:105–142.
53. Orme BK. *Getting Started With Conjoint Analysis: Strategies for Product Design and Pricing Research*. *Research Publishers*. 2006.
54. Bridges J, Mohamed AF, Finnern HW, et al. Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. *Lung Cancer*. 2012;77:224–231.
55. Peay HL, Hollin I, Sheffer H, Bridges J. Measuring treatment preferences of children with Duchenne muscular dystrophy using best-worst scaling. Presented at the 63rd Annual Meeting of the American Society of Human Genetics; October 23, 2013; Boston, Mass.
56. Deal K. Segmenting patients and physicians using preferences from discrete choice experiments. *Patient*. 2014;7:5–21.
57. Johnson FR, Hauber AB, Poulos CM. Research Report: A Brief Introduction to the Use of Stated-Choice Methods to Measure Preferences for Treatment Benefits and Risks. RTI Press publication No. RR-0009-0909. Research Triangle Park, NC: RTI International. http://www.rti.org/rtipress. Accessed December 20, 2013.

**Address correspondence to:** Holly L. Peay, MS, Parent Project Muscular Dystrophy, 401 Hackensack Avenue, 9th Floor, Hackensack, NJ 07601. E-mail: holly@parentprojectmd.org

# 4

# Caregiver preferences for emerging Duchenne muscular dystrophy treatments: A comparison of best-worst scaling and conjoint analysis

Patient
DOI 10.1007/s40271-014-0104-x

LEADING ARTICLE

# Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of Best-Worst Scaling and Conjoint Analysis

**Ilene L. Hollin · Holly L. Peay · John F. P. Bridges**



**Abstract**

*Background* Through Patient-Focused Drug Development, the US Food and Drug Administration (FDA) documents the perspective of patients and caregivers and are currently conducting 20 public meetings on a limited number of disease areas. Parent Project Muscular Dystrophy (PPMD), an advocacy organization for Duchenne muscular dystrophy (DMD), has demonstrated a community-engaged program of preference research that would complement the FDA's approach.

*Objective* Our objective was to compare two stated-preference methods, best-worst scaling (BWS) and conjoint analysis, within a study measuring caregivers' DMD-treatment preferences.

*Methods* Within one survey, two preference-elicitation methods were applied to 18 potential treatments incorporating six attributes and three levels. For each treatment profile, caregivers identified the best and worst feature and intention to use the treatment. We conducted three analyses to compare the elicitation methods using parameter estimates, conditional attribute importance and policy simulations focused on the 18 treatment profiles. For each, concordance between the results was compared using Spearman's rho.

*Results* BWS and conjoint analysis produced similar parameter estimates ($p < 0.01$); conditional attribute importance ($p < 0.01$); and policy simulations ($p < 0.01$). Greatest concordance was observed for the benefit and risk parameters, with differences observed for nausea and knowledge about the drug—where a lack of monotonicity was observed when using conjoint analysis.

*Conclusions* The observed concordance between approaches demonstrates the reliability of the stated-preference methods. Given the simplicity of combining BWS and conjoint analysis on single profiles, a combination approach is easily adopted. Minor irregularities for the conjoint-analysis results could not be explained by additional analyses and needs to be the focus of future research.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40271-014-0104-x) contains supplementary material, which is available to authorized users.

I. L. Hollin · J. F. P. Bridges (✉)
Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 624 N. Broadway, Rm 689, Baltimore, MD 21205, USA
e-mail: jbridge7@jhu.edu

I. L. Hollin
e-mail: ihollin1@jhu.edu

H. L. Peay
Parent Project Muscular Dystrophy, 401 Hackensack Ave 9th Floor, Hackensack, NJ 07601, USA
e-mail: holly@parentprojectmd.org

H. L. Peay · J. F. P. Bridges
Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA

Published online: 19 December 2014

| Key Points for Decision Makers |
| --- |
| The application of best-worst scaling (case 2), where treatment profiles are shown and respondents are asked to identify the best and worst attribute, allows for the addition of simple, complementary conjoint-analysis techniques to assess the intention to use potential therapies. |
| This approach is useful in regulatory decision making, especially in the context of rare diseases, where populations are limited and replication studies may be difficult. |
| The application of conjoint analysis techniques confirms our previous findings that caregivers of children with Duchenne muscular dystrophy will tolerate risks if emerging treatments can slow the progression of disease or extend the child's life. |

## 1 Introduction

Duchenne muscular dystrophy (DMD) is a rare neuromuscular disorder that occurs in 1.3–2.9 per 10,000 males [1–4]. Despite the burden of the disease [5–9], treatment is limited to off-label use of corticosteroids as there are no US FDA-approved therapies [1, 10–12]. This said, several potential therapies are under investigation [12, 13]. To inform regulatory review of these therapies, Parent Project Muscular Dystrophy (PPMD), an advocacy organization focused on finding a cure for DMD, led several collaborative efforts to advance regulatory science and decision making [14, 15]. This included applying stated-preferences methods to quantify caregiver preferences for benefits and risks [19]. Subsequently, PPMD submitted a patient-initiated FDA draft guidance for DMD in June 2014 that includes an engagement framework and guidance on the use of stated-preference methods to inform drug development and regulatory review [15].

These efforts are complementary with the FDA's effort to integrate the patient perspective in its drug development and approval process [16, 17]. The Patient Drug User Fee Act (PDUFA) V provides resources for dedicated review of patient input to extend patient influence beyond an advisory capacity [16]. The FDA initiated patient and caregiver engagement activities through a commitment to obtain the patient perspective, through Patient-Focused Drug Development public meetings, on 20 disease areas during the course of PDUFA V [16]. DMD was not one of the disease areas chosen, but the FDA noted that there are many more disease areas than can be addressed during the public meetings, and encouraged stakeholders to generate patient/caregiver input on their disease area that is relevant to the PDUFA commitments [18]. They have also sought expert guidance on measurement techniques for quantifying preferences [17].

PPMD responded to the FDA's encouragement to generate input through their community-engaged research program on DMD treatment preferences. Specifically, PPMD developed a framework for feasible community-engaged benefit-risk assessment that included best-worst scaling (BWS) [19]. BWS is a recently developed method that is used with increasing frequency in health research [20–28]. Here we aim to compare this approach with conjoint analysis, a more common stated-preference technique [29]. Specifically, we used a simple form of conjoint analysis that asks respondents if they would accept each of the profiles shown in the BWS experiment.

In BWS, respondents are asked to consider a profile and to select the best and the worst attribute [30]. There are different variations of BWS. A BWS object case (case 1) assesses relative preferences for a series of items that could otherwise be evaluated with a rating scale [30]. A BWS profile case (case 2) asks respondents to evaluate one profile at a time and therefore offers greater comparability to discrete-choice experiments or choice-based conjoint analysis [30]. Regardless of type, collecting two responses (best and worst choice) elicits more data about the respondent's preferences for items than can be obtained through conjoint analysis, which asks respondents to accept or reject a given commodity under a set of conditions [31]. The essential assumption is that the choice of the best and worst item represents the farthest difference between the degree of importance among any items on an underlying ranking of item importance [32]. BWS places greater emphasis on item importance, whereas conjoint analysis emphasizes trade-offs and more closely represents a real decision [33].

Previous studies have validated preference elicitation methods against a conjoint analysis task [32, 34]. Past studies comparing BWS and more established preference elicitation methods report mixed results [35–38]. Comparisons have found that the BWS object case has advantages over other methods such as superior discriminatory power without additional respondent burden and higher predictive validity [36]. An empirical comparison of BWS profile case and other discrete-choice experiments demonstrates that both methods produce similar preference patterns when rescaled [38]. To the best of our knowledge, there have been no empirical comparisons of a BWS profile case and a simple conjoint analysis where the respondent can accept or reject (i.e., opt out) a treatment.

In the experiment, we aimed to determine the acceptance of clinically relevant treatment options with varying

levels of benefits and risks. By including BWS and a conjoint analysis experiment, we aimed to exploit the complementary strengths of both types of experiments [39]. Specifically, incorporating the conjoint analysis question is useful because the BWS is limited in that it provides no information about preference for a given therapy [39]. The addition of the conjoint analysis question provides a second analysis that supports our BWS analysis, while also providing important independent data and psychological benefits to the respondents through asking about the most relevant endpoint—intention to use the treatment. The objective of this paper is to compare BWS and conjoint analysis to determine whether they produce similar results and to determine whether a combination approach is feasible and useful for quantifying benefits and risks in the context of treatment preferences. This has the potential to contribute both to the methodological literature on using BWS in health and to advancing our understanding of treatment preferences for rare disorders.

## 2 Methods

The study was conceptualized and designed by a collaborative team consisting of members of PPMD and a team of academic collaborators [19]. The study was part of a larger effort intended to explore DMD-related worries and preferences for treatment options among caregivers of children with DMD. The components to the study included a BWS experiment for analysis of worry prioritization (object case) and an experiment that included both conjoint analysis of therapy acceptance and BWS for measuring treatment preferences (profile case). The former is not described here.

The study, which was reviewed and deemed exempt by the Western Institutional Review Board, drew from a sample that was recruited using PPMD and Duchenne-Connect, a disease-specific patient registry for patients with DMD. In addition, snowball recruitment was used. Study participants were eligible if they were aged at least 18 years, a caregiver for at least one child living with DMD, living in the USA, and able to complete an online survey in English. The survey included basic demographic questions about the caregivers and affected children, including a disease progression item that represented impact of the disease on the child's function.

### 2.1 Experimental Design

Using a community-engaged approach, the research team identified six relevant treatment attributes, or categories of

**Fig. 1** Survey instrument example task: combined best-worst scaling and conjoint analysis

Choose the best thing by clicking the circle under "best" and choose the worst thing by clicking the circle under "worst." You have to choose a best thing and a worst thing to move on. Remember that a computer chose combinations to make the experiment work, and some of them seem bad. Even so, please pick the best and worst thing.

| Best | Treatment | Worst |
|---|---|---|
| o | Slows the progression of weakness | o |
| o | 2 year gain in expected lifespan | o |
| o | 1 year of post-approval drug information available | o |
| o | Causes loss of appetite | o |
| o | Increased risk of bleeding gums and increased bruising | o |
| o | Increased risk of harmless heart arrhythmia | o |

| If this treatment were real, would you use it for your child? | |
|---|---|
| o | Yes |
| o | No |
| o | I don't know |

characteristics (shown in Table 2), each with three levels. The levels indicate varying degrees of change to represent no increased risk, mild to moderate risks, or severe risks; and no change, modest change, and moderate change in benefit [19]. The development of the attributes and levels was informed by multiple stakeholders, an oversight group, and the study team. Additional details on this community-engaged, multi-stakeholder approach have been previously published [19]. The final selection of attributes and levels is reasonable considering the current pipeline of potential DMD therapies, with the exception of the highest risk levels that represent much greater risk than what has been associated with therapies in trial.

We systematically designed each of the hypothetical treatment options to vary among three levels across the six attributes to form a BWS experiment (profile case) [40]. We applied a 3^6 main effects orthogonal design, identified from the SAS database of orthogonal arrays [41]. Orthogonal designs focus on statistical efficiency and are commonly used and accessible methods [42, 43]. The minimum number of treatment profiles necessary to ensure no correlations between the attributes was 18 [44].

We presented the 18 potential treatment profiles in the experiment such that each treatment profile could be considered separate from the rest. We elicited treatment preference using BWS by asking caregivers what parts of each treatment profile they considered to be the best and the worst. For each treatment profile, immediately following the BWS choice task, we asked the respondents an additional conjoint analysis choice question—if they would use the treatment for their child if it were available (and under the hypothetical scenario of no out-of-pocket costs and the treatment being provided by their physician rather than as part of a clinical trial). Their choice set for answers were 'yes', 'no', and 'I don't know'. Figure 1 illustrates an example of the paired BWS and conjoint analysis task from the survey instrument.

### 2.2 Statistical Analysis

We ran three types of analyses to compare the result from the two elicitation formats. Specifically, we compared all parameter estimates and the conditional attribute importance, and conducted comparative policy analysis.

First, we calculated parameter estimates for each level of each attribute, facilitated by effects coding the data. In the BWS analysis, we used conditional logistic regression, with the dependent variable as the participants' choice of best and worst feature of each profile, again using effect coding [21]. Using logistic regression for the conjoint analysis, the dependent variable was the participant's choice to accept or reject the therapy represented by the treatment profile. We analyzed the respondent's choice set dichotomously by combining 'no' and 'I don't know' into one response group. There is no consensus on the use of a 'don't know' response in discrete-choice experiments, but this conservative approach is reasonable because, in a real-world scenario, indecision defaults to rejection; and in an experimental setting when forced to choose, respondents resort to 'no' [45, 46]. We analyzed the data using robust standard error to account for clustering at the individual level. To illustrate concordance, we both reported and plotted the parameter estimates to visually examine the patterns. Given the natures of the respective regressions for the BWS and conjoint analysis data, it is important to note that the results are on different scales. Rather than normalize these scales, we compared these estimates using Spearman's rho (although Pearson's rho gives similar, if not more convincing, results).

Second, we estimated conditional attribute importance for both methods by calculating the difference between the highest and lowest parameter estimates for each attribute

**Table 1** Characteristics of participants and affected child(ren) ($n = 119$)

| Participant characteristics | Mean (SD) or %[a] |
|---|---|
| Participant | |
| Caregiver age, years | 43.7 (7.7) |
| Child age, years | 12.1 (6.4) |
| Caregiver | |
| Relationship to child(ren) | |
| Mother | 70.6 |
| Father | 29.4 |
| Marital status | |
| Married/long-term relationship | 89.9 |
| Caucasian race | 91.6 |
| Education | |
| Less than 4-year college degree | 31.1 |
| 4-year college degree | 42.9 |
| Graduate/professional degree | 25.2 |
| Income | |
| <$50,000 | 14.3 |
| $50,000–100,000 | 37.0 |
| >$100,000 | 47.1 |
| Child | |
| One affected child | 92.4 |
| Participated in clinical research/trial | 92.0 |
| Ambulatory | 63.9 |

Ambulatory = ability to walk independently outside for at least short distances

[a] Data are presented as mean (standard deviation) or percentage

and dividing it by the sum of all differences. Calculating the importance of each attribute is a function of the levels chosen within the experiment, rather than being more generalizable. This said, both elicitation formats in this study used the same profiles, defined across the same level, and hence offer a valid method for comparison. Again, the relative concordance between the two sets of conditional importance was compared using Spearman's rho.

Finally, we conducted comparative policy analysis across the 18 profiles that were presented in the choice tasks. For the conjoint analysis, we simply used the probabilities that caregivers accepted each of the 18 profiles. These probabilities would provide an indication of intention to use particular drugs, which provides practical and policy-relevant information. For the BWS, we calculated 'net utilities' for each treatment profile from the BWS experiment. These represent overall value of an entire profile rather than for an individual item. To calculate net utilities, we applied the BWS item parameter estimates from the regression results and applied them to the items making up each treatment profile. The sum of the parameter estimates for each treatment profile represents the net utility for that treatment profile. These net utilities were compared with the probabilities of acceptance using Spearman's rho.

## 3 Results

Excluding five caregivers who did not complete the experiment, the final analytic sample consisted of the 119 caregivers who completed the entire survey. The mean age of survey respondents was 43.7 years (standard deviation [SD] 7.7), and most were biological mothers looking after one affected child living in the home. Caregivers also tended to be highly educated and high-income earners, with 68 % of the sample having at least a college degree and almost half of the sample (47 %) having an income of over $US100,000 per year. More than 90 % reported that their child had participated in clinical research or a clinical trial. See Table 1 for characteristics of participants and affected children.

Results of the BWS experiment using best-minus-worst scoring (maximum difference) have been published previously [19]. For comparison purposes with conjoint analysis (see Table 2), we present BWS results using conditional

**Table 2** Comparison of best-worst scaling and conjoint analysis results

| Attributes and levels | Best-worst scaling | | Conjoint analysis | |
|---|---|---|---|---|
| | Coefficient | SE | Coefficient | SE |
| Effect on muscle function | | | | |
| Stops the progression of weakness | 0.860 | 0.08 | 1.447 | 0.07 |
| Slows the progression of weakness | 0.353 | 0.07 | 1.161 | 0.08 |
| Does not change the progression of weakness | −1.213 | 0.12 | −2.608 | 0.13 |
| Lifespan | | | | |
| 5-year gain in expected lifespan | 0.581 | 0.07 | 0.942 | 0.06 |
| 2-year gain in expected lifespan | 0.118 | 0.06 | 0.717 | 0.06 |
| No extra gain in expected lifespan | −0.698 | 0.08 | −1.658 | 0.09 |
| Knowledge about the drug | | | | |
| 2 years of post-approval drug information available | −0.187 | 0.08 | 0.301 | 0.05 |
| 1 year of post-approval drug information available | 0.168 | 0.05 | 0.066 | 0.04 |
| No post-approval drug information available | 0.019 | 0.08 | −0.366 | 0.07 |
| Nausea | | | | |
| No increased change of nausea | −0.185 | 0.07 | 0.707 | 0.06 |
| Causes loss of appetite | 0.164 | 0.06 | 0.070 | 0.05 |
| Causes loss of appetite with occasional vomiting | 0.021 | 0.08 | −0.777 | 0.06 |
| Risk of bleed | | | | |
| No increased risk of bleeds | 0.772 | 0.08 | 1.429 | 0.06 |
| Increased risk of bleeding gums and increased bruising | 0.268 | 0.07 | 0.302 | 0.06 |
| Increased risk of hemorrhagic stroke and lifelong disability | −1.039 | 0.11 | −1.731 | 0.08 |
| Risk of heart arrhythmia | | | | |
| No increased risk of heart arrhythmia | 0.716 | 0.08 | 1.280 | 0.06 |
| Increased risk of harmless heart arrhythmia | 0.417 | 0.07 | 0.724 | 0.07 |
| Increased risk of dangerous arrhythmia and sudden death | −1.133 | 0.11 | −2.004 | 0.09 |

*SE* standard error

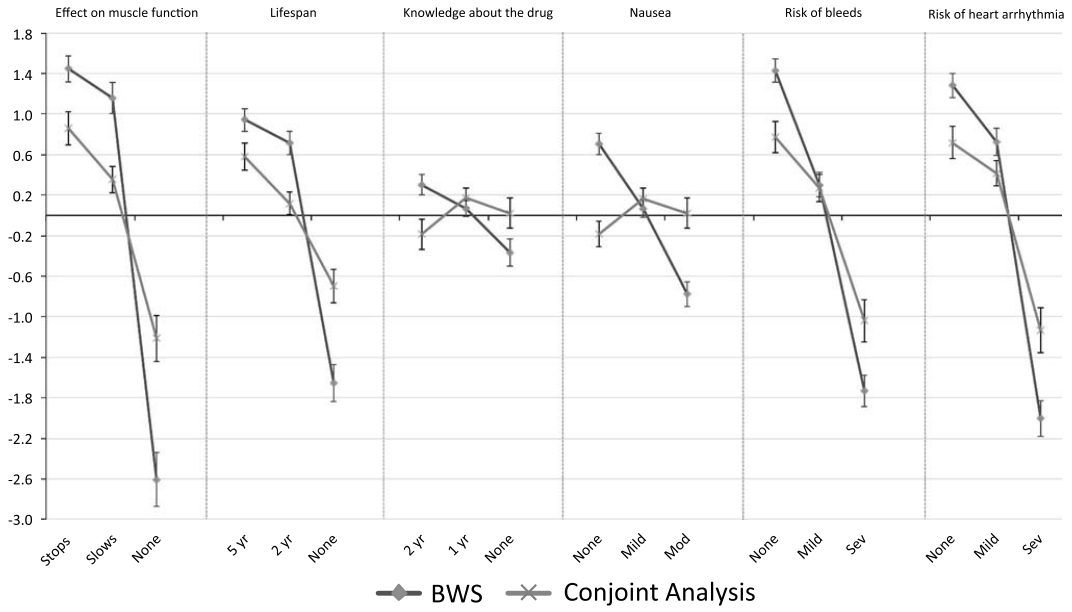



**Fig. 2** Comparison of parameter estimates based on best-worst scaling and conjoint analysis. *BWS* best-worst scaling

logit analysis, the results of which are relatively consistent with the best-worst scaling results [19]. Overall, the parameter estimates from the two elicitation formats were concordant (Spearman's $\rho = 0.907$; $p < 0.01$). Figure 2 presents a graphical representation comparing preference weights across the two methods.

Table 3 presents the conditional attributes importance for each attribute, using both BWS and conjoint analysis. The conditional attribute importance was 27 % for stopping/slowing the progression of weakness across both studies, 21 and 23 % for risk of bleed, and 21 and 24 % for risk of heart arrhythmia for the BWS and conjoint analysis experiments, respectively (see Table 3). The conditional attribute importance was concordant across BWS and conjoint analysis; the Spearman's rho was 0.943 ($p < 0.01$).

Finally, the concordance between BWS and conjoint analysis was again confirmed through comparative policy analysis, and rank ordering was concordant ($p < 0.01$). As seen in Table 4, the four treatment profiles with the highest net utilities all had a probability of acceptance greater than 80 % from the conjoint experiment. This concordance demonstrates the complementary nature between the two methods. It is clear that the net utility estimates for a given treatment profile, derived from the BWS parameter estimates, corresponds to the probability of intention to accept a specific therapy. Similarly, the four profiles with the lowest net utilities all had a probability of acceptance less than 20 % from the conjoint experiment.

## 4 Discussion

We evaluated the concurrent use in the same survey of a conjoint analysis experiment with a BWS experiment, and compared the results. Our data indicate that the two methods are concordant, particularly in terms of individual item parameter estimates for the benefits and risks (see Fig. 2), conditional attribute importance (see Table 3), and net utility of treatment profiles compared with probabilities of accepting the treatment (see Table 4). The items with the highest and lowest utility are remarkably consistent across methods, and the treatment profiles most and least accepted are concordant with the treatments with the highest and lowest net utility.

We observed some important differences using the two methods. This is most apparent when looking at the parameter estimates for the attributes 'knowledge about the drug' and 'nausea', in which the graph (Fig. 2) is not monotonic but changes direction. The highest-level benefit for 'knowledge about the drug' (2 years of post-market information) has a part-worth utility observed using BWS of 0.30 ($p < 0.05$), while using conjoint analysis it is $-0.19$ ($p < 0.05$). For the lowest level of 'nausea' (none), the observed part-worth utility for BWS is 0.71 ($p < 0.05$), and for conjoint analysis it is $-0.18$ ($p < 0.05$). In these two instances, the rank order of attribute importance flips (Table 3). We conducted two post hoc analyses (stratified analysis based on disease severity and two-group latent

**Table 3** Comparison of conditional attribute importance

| | Conditional attribute importance (%) | |
|---|---|---|
| | Best-worst scaling | Conjoint analysis |
| Effects on muscle function | 26.6 | 26.9 |
| Lifespan | 17.1 | 16.6 |
| Knowledge about the drug | 4.4 | 4.6 |
| Nausea | 9.7 | 4.5 |
| Risk of bleeds | 20.7 | 23.5 |
| Risk of heart arrhythmia | 21.5 | 23.9 |
| Total | 100 | 100 |

class analysis to identify subtypes based on associations with the responses) to attempt to explain the heterogeneity in item acceptance. Disease severity was defined in terms of ambulation status, in which children were considered to be ambulatory if they could walk independently outdoors for short distances (such as to the car) or if they were too young to walk. The lack of monotonicity for these two items in the conjoint analysis could not be explained by post hoc analysis, leading us to assume that it was due to an unobserved framing effect, where participants may have reacted to a particular choice in different ways depending on whether it was presented as a loss or as a gain.

Alternatively, the differences between the two methods indicate that, while respondents value knowledge about the drug and nausea, these variables may not impact the actual choices that caregivers may make. Future research should evaluate differences between these two methods, and across other elicitation methods such as more traditional paired-profile conjoint analysis methods.

The data on the intention of caregivers to accept or reject particular treatments not only provided complementary data to BWS, but also relevant information for industry and regulators regarding the proportion of caregivers who might use therapies with different benefit–risk profiles. The results suggest that a large percentage of parents anticipate using a drug that would stop the progression of weakness, even given a loss of appetite and occasional vomiting together with an increased risk for mild bleeds. In contrast, about one-third anticipate using a drug that includes two serious risks, even given the highest benefits (stops progression and 5-year gain in lifespan). Less than 20 % anticipate using a drug that offers a 2-year gain in lifespan with no benefit to weakness, when associated with one serious risk.

The next phases of PPMD's ongoing preferences studies will allow us to address some of the limitations associated with this study. This sample of caregivers tended to be highly educated and earning high incomes. Future research will utilize large samples of a more diverse group of caregivers to be adequately powered for adjusted logistic regression models and to investigate the heterogeneity in the sample. In this study, presenting the BWS experiment before the conjoint analysis experiment may have affected the results, as may the order of presentation for the

**Table 4** Comparative policy analysis

| Profile # | Probability accept | Net utility | Effect on muscle function | Lifespan | Knowledge about the drug | Nausea | Risk of bleed | Risk of heart arrhythmia |
|---|---|---|---|---|---|---|---|---|
| 18 | 0.96 | 6.106 | Stops | 5 year | 2 year | None | None | None |
| 11 | 0.84 | 3.040 | Slows | 2 year | 1 year | Mild | Mild | Mild |
| 7 | 0.82 | 1.646 | Stops | None | None | Mild | None | Mild |
| 15 | 0.81 | 3.444 | Slows | 2 year | None | Mod | None | None |
| 1 | 0.78 | 0.660 | Stops | None | 1 year | Mod | Mild | None |
| 6 | 0.67 | −0.224 | None | 5 year | 1 year | Mod | None | Mild |
| 17 | 0.64 | −0.380 | None | 5 year | None | Mild | Mild | None |
| 16 | 0.55 | 0.681 | Stops | 2 year | 2 year | Mod | Severe | Mild |
| 9 | 0.52 | 1.437 | Slows | 5 year | None | None | Severe | Mild |
| 4 | 0.48 | 0.803 | Stops | 2 year | None | None | Mild | Severe |
| 2 | 0.46 | −0.075 | Slows | 5 year | 2 year | Mod | Mild | Severe |
| 10 | 0.34 | −0.299 | Slows | None | 1 year | None | None | Severe |
| 12 | 0.33 | −0.577 | Slows | None | 2 year | Mild | Severe | None |
| 3 | 0.32 | −1.210 | Stops | 5 year | 1 year | Mild | Severe | Severe |
| 8 | 0.18 | −1.569 | None | 2 year | 1 year | None | Severe | None |
| 13 | 0.18 | −2.095 | None | 2 year | 2 year | Mild | None | Severe |
| 14 | 0.09 | −2.232 | None | None | 2 year | None | Mild | Mild |
| 5 | 0.05 | −9.144 | None | None | None | Mod | Severe | Severe |

treatment options and attributes/levels. In future research, we can randomize the order of the experiments and the presented treatment options.

A potential limitation of conjoint analysis is that it is subject to ceiling or floor effects. However, we calculated the probabilities that caregivers would accept or reject a therapy given a particular treatment profile. As seen in Table 4, the variability in probability of taking the treatment across treatment profiles, and the fact that no treatment was universally accepted or rejected, indicates that caregivers responded to the experiment reasonably and made appropriate trade-offs when considering their choice.

A final limitation is that we compare BWS using the conditional logit analytic approach, which is more computationally intensive than the maximum difference analytic approach. Previously we analyzed the data using both approaches [21, 47], and, since they are highly correlated [20, 26], we presented results from the more accessible maximum difference approach [19]. Given that we conducted the BWS analysis two ways, rescaled the parameters and calculated correlations to find the two analytic approaches to BWS to be virtually identical [19], we felt confident that using the conditional logit analytic approach for comparing BWS with conjoint analysis would not qualitatively change the results.

## 5 Conclusions

This study demonstrates the concordance in the preferences estimated via two stated-preference techniques, BWS and a simple conjoint analysis. Substantively, this provides important confirmation of our previously published results on caregivers' benefit–risk trade-offs for DMD therapies. The combination of BWS and conjoint analysis experiments in a single survey is a useful approach because it allows for the interpretation and application of the data to understand risk tolerance, meaningful benefits, and explore intention to use specific therapies. Our data support the utility of this combination approach for treatment preferences research that is intended to inform regulatory decision making.

These results and the method we propose have important implications for patient-centered drug development. Experiments using BWS together with conjoint analysis might be especially useful in quantifying patient and caregiver preferences. These combined experiments produce results that inform sponsors, regulators, and the broader rare disorder community. They are especially important in the case of progressive, life-threatening conditions with limited treatment options, where regulators may be less able to imagine how a 'typical' patient or caregiver might weigh benefits and risks. The ongoing benefit–risk research led by PPMD demonstrates that patient and disease advocacy groups can contribute to the literature on benefit–risk, while also providing leadership in furthering community-centered approaches and scientific methodologies to advance the FDA's commitment to promoting transparency in benefit–risk assessment and patient-centered drug development.

**Acknowledgments** The authors appreciate the leadership and commitment of the Parent Project Muscular Dystrophy oversight committee: Pat Furlong, Brian Denger, Sharon Hesterlee, and Kathi Kinnett. We are indebted to the stakeholder informants, parents who participated in the cognitive interviews, and caregivers who completed the survey. This paper was presented at the first meeting of the International Academy for Health Preference Research (IAHPR), 8 November 2014. We are grateful for the feedback we received from the participants of this meeting and of the peer reviewers of this manuscript. This study was conducted with the support from PPMD. Dr. Bridges also acknowledges support from the Patient-Centered Outcomes Research Institute (PCORI) Methods Program Award (ME-1303-5946). ILH conducted data analyses and wrote the manuscript. JFPB and HP conceived and designed the study, analysis plan, and assisted in the writing and reviewing of the manuscript. All authors reviewed and approved the final draft of this manuscript. JFPB acts as the overall guarantor of this article.

**Conflict of interest** Holly Peay is an employee of PPMD and John Bridges was hired as a consultant by PPMD to provide methodological expertise. The authors have no conflicts to disclose.

## References

1. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9(1):77–93.
2. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12(10):926–9.
3. Center for Disease Control and Prevention (CDC). Prevalence of Duchenne/Becker muscular dystrophy among males aged 5–24 years—Four states, 2007. MMWR Morb Wkly Rep. 2009; 58:1119–22.
4. Emery AE. Population frequencies of inherited neuromuscular diseases—a world survey. Neuromuscul Disord. 1991;1(1):19–29.
5. Pangalila RF, van den Bos GA, Stam HJ, van Exel NJA, Brouwer WB, Roebroeck ME. Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. Disabil Rehabil. 2012;34(12):988–96.
6. Kenneson A, Bobo JK. The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. Health Soc Care Commun. 2010;18(5):520–8.
7. Larkindale J, Yang W, Hogan PF, Simon CJ, Zhang Y, Jain A, et al. Cost of illness for neuromuscular diseases in the United States. Muscle Nerve. 2014;49(3):431–8.
8. Ouyang L, Grosse SD, Kenneson A. Health care utilization and expenditures for children and young adults with muscular dystrophy in a privately insured population. J Child Neurol. 2008;23(8):883-8.

9. Ouyang L, Grosse SD, Fox MH, Bolen J. A national profile of health care and family impacts of children with muscular dystrophy and special health care needs in the United States. J Child Neurol. 2012;27(5):569–76.
10. Angelini C. The role of corticosteroids in muscular dystrophy: a critical appraisal. Muscle Nerve. 2007;36(4):424–35.
11. Bushby K, Muntoni F, Urtizberea A, Hughes R, Griggs R. Report on the 124th ENMC International Workshop. Treatment of Duchenne muscular dystrophy; defining the gold standards of management in the use of corticosteroids 2–4 April 2004, Naarden, The Netherlands. Neuromuscul Disord. 2004;14(8): 526–34.
12. Biggar W, Harris V, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscular Disord. 2006;16(4):249–55.
13. Govoni A, Magri F, Brajkovic S, Zanetta C, Faravelli I, Corti S, et al. Ongoing therapeutic trials and outcome measures for Duchenne muscular dystrophy. Cell Mol Life Sci. 2013;70(23):4585–602.
14. Parent Project Muscular Dystrophy. Putting Patients First: Recommendations to speed responsible access to new therapies for Duchenne muscular dystrophy and other rare, serious and life-threatening neurologic disorders. Hackensack; 2013.
15. Parent Project Muscular Dystrophy. Guidance for Industry: Duchenne Muscular Dystrophy Developing Drugs for Treatment over the Spectrum of Disease. Hackensack; 2014.
16. U.S. Food and Drug Administration. Enhancing Benefit-Risk Assessment in Regulatory Decision-Making. Silver Spring; 2014. http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm. Accessed June 26 2014.
17. Mullard A. Patient-focused drug development programme takes first steps. Nat Rev Drug Discov. 2013;12(9):651–2.
18. "Prescription Drug User Fee Act Patient-Focused Drug Development; Announcement of Disease Areas for Meetings Conducted in Fiscal Years 2013–2015". Federal Register 2013; 78:21613–4.
19. Peay HL, Hollin I, Fischer R, Bridges JF. A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. Clin Ther. 2014;36(5):624–37.
20. Louviere JJ, Flynn TN. Using best-worst scaling choice experiments to measure public perceptions and preferences for healthcare reform in Australia. Patient. 2010;3(4):275–83.
21. Molassiotis A, Emsley R, Ashcroft D, Caress A, Ellis J, Wagland R, et al. Applying best-worst scaling methodology to establish delivery preferences of a symptom supportive care intervention in patients with lung cancer. Lung Cancer. 2012;77(1):199–204.
22. Marti J. A best-worst scaling survey of adolescents' level of concern for health and non-health consequences of smoking. Soc Sci Med. 2012;75(1):87–97.
23. Flynn TN, Louviere JJ, Peters TJ, Coast J. Estimating preferences for a dermatology consultation using best-worst scaling: comparison of various methods of analysis. BMC Med Res Methodol. 2008;8(1):76.
24. Swancutt DR, Greenfield SM, Wilson S. Women's colposcopy experience and preferences: a mixed methods study. BMC Womens Health. 2008;8(1):2.
25. Coast J, Salisbury C, De Berker D, Noble A, Horrocks S, Peters T, et al. Preferences for aspects of a dermatology consultation. Br J Dermatol. 2006;155(2):387–92.
26. Gallego G, Bridges JFP, Flynn T, Blauvelt BM, Niessen LW. Using best-worst scaling in horizon scanning for hepatocellular carcinoma technologies. Int J Technol Assess Health Care. 2012;28(03):339–46. doi:10.1017/S026646231200027X.
27. Finn A, Louviere JJ. Determining the appropriate response to evidence of public concern: the case of food safety. J Public Policy Market. 1992:12–25.
28. Marley AA, Louviere JJ. Some probabilistic models of best, worst, and best-worst choices. J Math Psychol. 2005;49(6):464–80.
29. Bridges J, Kinter E, Kidane L, Heinzen R, McCormick C. Things are looking up since we started listening to patients: recent trends in the application of conjoint analysis in health 1970–2007. Patient. 2008;1(4):273–82.
30. Flynn TN. Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. Expert Rev Pharmacoecon Outcomes Res. 2010;10(3):259–67.
31. Ryan M, Watson V, Amaya-Amaya M. Methodological issues in the monetary valuation of benefits in healthcare. Expert Rev Pharmacoecon Outcomes Res. 2003;3(6):717–27.
32. Louviere JJ, Islam T. A comparison of importance weights and willingness-to-pay measures derived from choice-based conjoint, constant sum scales and best-worst scaling. J Bus Res. 2008;61(9):903–11.
33. Klose T. The contingent valuation method in health care. Health Policy. 1999;47(2):97–123.
34. Srinivasan V. A conjunctive-compensatory approach to the self-explication of multiattributed preferences. Dec Sci. 1988;19(2): 295–305.
35. Jaeger SR, Jørgensen AS, Aaslyng MD, Bredie WL. Best–worst scaling: an introduction and initial comparison with monadic rating for preference elicitation with food products. Food Qual Prefer. 2008;19(6):579–88.
36. Cohen S, Orme B. What's your preference? Market Res. 2004;16(2):32–7.
37. Cohen S, editor. Maximum difference scaling: improved measures of importance and preference for segmentation. Sawtooth Software Conference Proceedings, Sawtooth Software, Inc; 2003.
38. Potoglou D, Burge P, Flynn T, Netten A, Malley J, Forder J, et al. Best–worst scaling vs. discrete choice experiments: an empirical comparison using social care data. Soc Sci Med. 2011;72(10):1717–27.
39. Flynn TN, Louviere JJ, Peters TJ, Coast J. Best–worst scaling: what it can do for health care research and how to do it. J Health Econ. 2007;26(1):171–89.
40. Bridges JF, Kinter ET, Schmeding A, Rudolph I, Mühlbacher A. Can patients diagnosed with schizophrenia complete choice-based conjoint analysis tasks? Patient. 2011;4(4):267–75.
41. Kuhfeld W. Orthogonal arrays [TS-723]. Cary: SAS [online]. 2010.
42. Kinter ET, Prior TJ, Carswell CI, Bridges JF. A comparison of two experimental design approaches in applying conjoint analysis in patient-centered outcomes research. Patient. 2012;5(4):279–94.
43. Bridges JF, Kinter ET, Kidane L, Heinzen RR, McCormick C. Things are looking up since we started listening to patients. Patient. 2008;1(4):273–82.
44. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Mühlbacher A, Regier DA et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force. Value Health. 2013;16(1):3–13.
45. Carson RT, Hanemann WM, Kopp RJ, Jon AK, Robert Cameron M, Presser S et al. Referendum design and contingent valuation: the NOAA panel's no-vote recommendation. Rev Econ Stat. 1998;80(2):335–8.
46. Groothuis PA, Whitehead JC. Does don't know mean no? Analysis of "don't know" responses in dichotomous choice contingent valuation questions. Appl Econ. 2002;34(15):1935–40.
47. McFadden D. Conditional logit analysis of qualitative choice behavior. In: Zarembka P, editor. Frontiers in econometrics. New York: Academic Press; 1974. p. 105–42.

# 5

# Prioritizing parental worry associated with Duchenne muscular dystrophy using best-worst scaling

**CHAPTER 5.**

# Prioritizing Parental Worry Associated with Duchenne Muscular Dystrophy using Best-Worst Scaling

Peay HL[1,2], Hollin IL[3], Bridges JFP[3]

1. Parent Project Muscular Dystrophy
Hackensack, NJ, USA

2. Department of Clinical Genetics
Leiden University Medical Centre
Leiden, The Netherlands

3. Department of Health Policy and Management
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

**ABSTRACT**

Duchenne muscular dystrophy (DMD) is a progressive, fatal pediatric disorder with significant burden on parents. Assessing disease impact can inform clinical interventions.

Best-worst scaling (BWS) was used to elicit parental priorities among 16 short-term, DMD-related worries identified through community engagement. Respondents viewed 16 subsets of worries, identified using a balanced, incomplete block design, and identified the most and least worrying items. Priorities were assessed using best-worst scores (spanning +1 to -1) representing the relative number of times items were endorsed as most and least worrying. Independent-sample t-tests compared prioritization of parents with ambulatory and non-ambulatory children.

Participants (n=119) most prioritized worries about weakness progression (BW score 0.64 $p<0.001$) and getting the right care over time (0.25, $p<0.001$). Compared to parents of non-ambulatory children, parents of ambulatory children more highly prioritized missing treatments (0.31 vs. 0.13, $p<0.001$) and being a good enough parent (0.06 vs. -0.08, $p=0.01$), and less prioritized child feeling like a burden (-0.24 vs. -0.07, $p<0.001$).

Interventions to reduce negative parental impact may be most effective in conjunction with care-related interventions for the child, regardless of disease stage. We demonstrate an accessible, clinically-relevant approach to prioritize disease impact using BWS, which offers an alternative to the use of traditional rating/ranking scales.

**INTRODUCTION**

Understanding patients' and caregivers' experience of disease impact has implications for clinical care provision, public health programs, and policy development. The associations of perceived disease impact with health and psychosocial outcomes are well-described (for example, see Baines and Wittkowski 2013; McAndrew et al. 2014). Quantifying patients'/caregivers' preferences is an important issue for clinicians (dosReis et al 2014; Black 2013) and models of patient-centered care (Haywood 2006) and shared decision making (Politi and Street 2011) mark an increasing focus on assessing patients'/caregivers' perspectives and using the resulting data to inform healthcare delivery and decision making. Measuring patients'/caregivers' views avoids clinician/researcher bias and encourages a focus on reducing

symptoms, minimizing disability, and improving quality of life (Black 2014). Special attention to disease impact is included in the Food and Drug Administration's Patient-Focused Drug Development Program (U.S. Food and Drug Administration), raising the visibility and importance of assessing impact of disease for clinical trial sponsors and disease community stakeholders. These concepts are familiar to genetic counselors, for whom exploring a clients' lived experience is defined as a Practice-Based Competency (Accreditation Counsel for Genetic Counseling 2013).

In research settings, disease impact is often assessed using qualitative approaches or standard quantitative measures of severity, burden, and quality of life. In the regulatory context, patient and caregiver testimonial is another common approach. Each approach comes with strengths and limitations. Qualitative approaches are excellent for obtaining a deep and nuanced understanding of disease impact and often generate hypotheses to be tested in a generalized population in subsequent studies, while quantitative research using validated measures allow generalizable data to be systematically collected and compared across populations (Creswell et al. 2011; Razafsha et al. 2012). In this study we employed a quantitative stated preferences method, best-worst scaling (BWS), to prioritize disease impact in Duchenne muscular dystrophy (DMD).

Duchenne muscular dystrophy (DMD) is a rare, life-threatening disorder with pediatric onset (Bushby et al. 2010). Affected individuals, primarily males, have progressive loss of functional muscle fibers that result in weakness, loss of ambulation that typically occurs in the teen years, and premature death in the 20s-30s (Bushby et al. 2010; Flanigan 2014). Though the use of corticosteroids and advances in respiratory support and cardiac care have substantially impacted the health of individuals with DMD (Bushby et al. 2010; Eagle et al. 2002; Flanigan 2014), patients and parents are still faced with significant burden related to disease progression, ongoing care demands, and financial impact (Boyer et al. 2006; Daoud et al. 2004; Hatzmann et al. 2008; Kenneson and Bobo 2010; Landfeldt et al. 2014; Pangalila et al. 2012; Reid and Renwick 2001).

The study aimed to document parents' prioritization of short-term, disease specific worries when caring for an individual with DMD, and to identify if worry prioritization varies based on the child's ambulation status (representing disease progression). In addition, we describe parents'

physical and mental health status. Duchenne worry can be conceptualized as an emotion-focused illness representation, as defined by Leventhal's Common-Sense Model of Health and Illness Self-Regulation (McAndrew et al. 2008). The model proposes individuals as active problem-solvers who, when faced with a threat such as DMD in their children, engage in a dynamic process of developing and refining cognitive and emotion-focused illness representations that influence coping efforts (McAndrew et al. 2008). The data presented here are part of a larger project that also evaluated the treatment preferences of parent/guardian caregivers (Hollin et al. 2014; Peay et al. 2014a). An overarching objective of the research program was to model a replicable, community-engaged approach to obtaining preference and priority data from a sample of parents and guardians.

**METHODS**

A central aspect of the research program was the community-engaged approach that involved stakeholders in development of the survey instrument and dissemination of findings (Peay et al. 2014a). The study was lead by Parent Project Muscular Dystrophy (PPMD), an advocacy organization focused on finding a cure for Duchenne muscular dystrophy. A disease-community oversight team comprising PPMD staff (a clinician, a scientist experienced in drug development, and two caregivers of individuals with DMD) collaborated with the research team to design and implement the study.

We employed BWS Case 1 to prioritize worries when caring for an individual with DMD. Worry is defined as thoughts and images that are negatively affect-laden and relatively uncontrollable (Borkovec et al. 1983). Worry is clinically meaningful in that it may be related to an increase in behaviors that the worrier believes will protect his or her health, or in this case, the health of the child (McCaul and Goetz 2008); for example, Magnan and colleagues (2009) describe benefits of non-pathological worry that include motivation for positive health behaviors by increasing the salience of a health threat and acting as a cue to action.

BWS is a stated preference method grounded in Random Utility Theory that is based on how people make choices of extremes from within a choice set (Louviere and Flynn 2010). BWS Case 1, also known as the object case or object scaling, is relatively new to healthcare research (Flynn 2010). It is used to assess the relative preferences for a series of related items that could

otherwise be evaluated using a rating scale (Flynn 2010). In designing a BWS study a detailed set of related items, called attributes, are typically developed through qualitative stakeholder engagement (Bridges et al. 2011). The attribute set can be developed to include items that are each expected to be highly relevant to the majority of the study population. Instead of presenting these items as a scale and asking respondents for level of endorsement, which would likely result in highly skewed data and poor discriminative ability, BWS Case 1 quantifies prioritization among items selected to be highly relevant. Advantages of BWS over rating scales and ranking exercises have been summarized by Erdem and Rigby (2013).

In a BWS survey instrument, attributes are presented in subsets that are chosen based on a balanced incomplete block design (Ross et al. 2014) to ensure equal probability of selection for each attribute. The respondent is asked to select the most relevant or favorable (the “best”) and the least relevant or favorable (the “worst”) attribute among each subset. The underlying assumption is that this choice represents the farthest difference between the degree of importance among any items on an underlying ranking of item importance (Louviere and Islam 2008). An example choice task is shown in Figure I.

Consistent with our overarching objective, BWS represents a pragmatic methodology that allows deep understanding of one component of illness impact while also allowing quantitative ranking and group comparison. Though BWS is typically utilized to identify preferences among fact-based or cognitive attributes, there are examples of BWS being used to prioritize control-based and worry-based attributes, for example related to food safety (Erdem and Rigby 2013), and to prioritize among quality of life attributes (Flynn et al. 2007) that have affective components. By asking participants to choose among extremes, BWS minimizes the chances of introducing false assumptions about decision making (Flynn et al. 2007). BWS requires relatively low sample sizes, which is important for studies of rare disorder populations.

**INSTRUMENT DEVELOPMENT**

In designing the survey we used standards outlined in the ISPOR checklist for conjoint analysis (Bridges et al. 2011) and specific guidance on the use of BWS (Flynn 2010; Louviere and Flynn 2010). As described by Johnson and colleagues (2009), development of the attributes should include careful consideration of the disorder symptoms and severity; the target population

should be involved in development of attributes through qualitative methods; and the resulting experimental attributes should then be pilot tested and refined. However, to achieve our overarching aim of a replicable, feasible model, we were unable to employ extremely complex, time and resource intensive development processes, such as that described by Grewal and colleagues (2006). Instead we employed a pragmatic community engaged approach with input from a wide range of stakeholders.

PPMD invited stakeholder informants to participate in the survey development. We solicited open-ended responses from 5 highly-engaged parent advocates about their most important, current DMD-related worries. The parents were chosen to represent caregivers of children and adults with DMD of different ages and disease stages. The worry narratives provided by the parent informants were compiled, redundant items were eliminated, and statements were grouped under themes. These statements were evaluated, refined, and reduced by the PPMD oversight team and the study team, drawing on the diverse personal, clinical, and research experience of the teams; the determinations were informed by a review of the literature. The next step, thematic analysis and additional item reduction and refinement, resulted in a list of 16 worry items grouped under 4 worry domains—the child's affect and emotion; medical concerns about the child; family and social worries; and parent well-being. Patient advocates and experts representing neurology, clinical genetics, biopharmaceutical companies, and social/behavioral science reviewed and revised the items, which were finalized once no further amendments were suggested. Though there are no published studies specific to DMD-related worries, the final worry domains and items are supported by published literature about DMD impact and burden (Boyer et al. 2006; Daoud et al. 2004; Hatzmann et al. 2008; Kenneson and Bobo 2010; Landfeldt et al. 2014; Pangalila et al. 2012; Reid and Renwick 2001).
The final worry items were randomized into 16 combinations of response sets, each comprising 6 worry attributes. For each of the 16 combinations, participants were asked: "In the past 7 days, choose which you have been most worried about and which you have been least worried about." An example choice task is shown in Figure I.

**Figure I. Sample choice task**

For each list of worries, please tell us which one you have been most worried about in the past 7 days, and which one you have been least worried about in the past 7 days. Even if you are really worried about all of them, or not too worried about any of them, please choose the most and least worrying item. In the past 7 days, choose which you have been most worried about and which you have been least worried about.

| Most Worried | Worries | Least Worried |
|---|---|---|
| ○ | My child getting weaker | ○ |
| ○ | Managing my uncertainty about my child's future | ○ |
| ○ | Affording care my child needs within the family budget | ○ |
| ○ | Having time for myself | ○ |
| ○ | My child feeling happy | ○ |
| ○ | My child having good friends | ○ |

Cognitive interviews with seven parents of individuals with DMD of varying ages and disease stages were used to assess comprehension, refine terminology, and explore the acceptability of the instrument; this is described in detail elsewhere (Peay et al. 2014a). During the interviews,

participants endorsed the face validity of the worry items (i.e., the items represented their significant worries) and consistently indicated more difficulty choosing an item of least worry than and item of most worry, suggesting successful item development. The worry statements and domains are shown in Table I.

**Table I. Worry items and domains**

| Worry Item | Domain |
|---|---|
| My child getting weaker | **Medical concerns** |
| Getting the right care for my child over time | |
| My child missing out on new treatments | |
| Affording care my child needs within the family budget | |
| My child feeling happy | **Child affect/emotion** |
| My child having good friends | |
| My child not being able to express deep worries | |
| My child feeling like burden on the family | |
| Managing my uncertainty about my child's future | **Parent wellbeing** |
| Being a good enough parent for my child | |
| Me handling the emotional demands of Duchenne | |
| Having time for myself | |
| The wellbeing of my other children | **Family and social** |
| My child becoming independent from me over time | |
| Effect of Duchenne on my closest relationships | |
| Feeling isolated from other families | |

In addition to the BWS tasks, the survey included participant demographics and health status, measured using the SF-12 (Ware et al. 1996). The SF-12 is scored into Physical and Mental

Health Composite Scores (PCS and MCS, respectively) that range from 0 to 100, where a zero score indicates the lowest level of health and 100 indicates the highest level of health. Norm-based scoring facilitates interpretation in that individual respondent sores below 45 and group mean score below 47 are below the average population range (Optum SF-12v2 Health Survey: Advantages of Norm-Based Scoring). We also obtained information about the health status and care information for the child with DMD, including age, number of affected children in the family, ambulation status, prior research experience, and whether the child has experienced a life-threatening emergency.

**PARTICIPANTS**

Participants were parents or guardians of at least one living child with DMD. They lived in the United States, were at least 18 years of age, and were able to complete an online survey in English. The affected child could be any age or at any stage of disease.

The survey was administered online using the Qualtrics survey system from January 17, 2013 to February 21, 2013. Recruitment occurred using newsletter notices, social media, word-of-mouth, and through emails from Parent Project Muscular Dystrophy and the DuchenneConnect self-report registry. The anonymous survey was determined to be exempt by the Western Institutional Review Board (# 1-756840-1).

**DATA ANALYSIS**

The dependent variable in BWS is the participants' judgment about the extremes (in this case, most and least worrying items) in each profile that is presented to them (Molassiotis et al. 2012). The simplest analytic technique focuses on the number of times an attribute was chosen as best and as worst over all of the choice tasks. The analytic output, which we call the relative best-minus-worst (BW) score, can be calculated by subtracting the number of times a feature was chosen as worst from the number of times it was chosen as best, then dividing by the total number of times it was available to be chosen (Flynn et al. 2007).

Such simple methods have demonstrated a very high level of correlation with more complicated regression-based techniques (Gallego et al. 2012; Louviere and Flynn 2010). Like all techniques to estimate ordinal, multinomial outcomes, scoring assumes equal spacing between things that were chosen as best (BW score=1) and those chosen as worst (BW score=-1). The BW score is

estimated as a mean across the sample. This allows us to report the standard errors for these means and conduct t-tests to determine whether the scores were significantly different than zero. Additional information about the relative best-minus-worst analysis has been described elsewhere (Peay et al. 2014a).

Next, we conducted a stratified analysis by calculating BW scores for parents/guardians with ambulatory children and those with non-ambulatory children. We used Spearman's rho to compare the correlation of the rank order of worry items between the two groups. Finally, we conducted t-tests on BW scores for each worry, hypothesizing no statistically-significant differences across the ambulatory and non-ambulatory groups.

**RESULTS**

One hundred and nineteen caregivers who self-identified as being a parent or guardian of an individual with DMD included in the analysis. When dichotomized into an "ambulatory" group, defined as those who could walk independently outdoors for at least short distances, and a "non-ambulatory" group, defined as those who could not walk outdoors without help, 64% of children were in the ambulatory group and 36% in the non-ambulatory group. Table II summarizes the characteristics of the sample. Participants were predominately Caucasian, married, biological mothers, and had one affected child. There were no significant differences between the sample characteristics collected from the ambulatory and non-ambulatory groups except for ages of parent participants (M= 40.5, SD=6.1 for parents of ambulatory children versus M= 49.1, SD 7.1 for parents of non-ambulatory children, $p<0.01$) and their children (M= 8.8, SD 3.5 for ambulatory children versus M= 18.0, SD 6.3 for non-ambulatory children, $p<0.01$).

**Table II. Characteristics of participants and affected child(ren) by ambulation status**

| | Ambulatory (n=76) | Non-Ambulatory (n=43) | P-value |
|---|---|---|---|
| **Participant characteristics** | | | |
| Parent age in years | 40.5 (SD=6.1) | 49.1 (SD=7.1) | <0.01 |
| Child age in years | 8.8 (SD= 3.5) | 18.0 (SD=6.3) | <0.01 |
| **Parent characteristics** | | | |
| Relationship to child(ren) | | | |
| Biological mother | 68.4% | 65.1% | 0.72 |
| Biological father | 26.3% | 32.6% | 0.47 |
| Adoptive mother | 5.3% | 0.0% | 0.13 |
| Adoptive father | 0.0% | 2.3% | 0.18 |
| Marital status | | | |
| Married/long-term relationship | 93.4% | 83.7% | 0.09 |
| Divorced/Separated | 6.6% | 14.0% | 0.19 |
| Widowed | 0.0% | 2.3% | 0.18 |
| Race | | | |
| Caucasian | 89.5% | 95.3% | 0.27 |
| Education | | | |
| High school/GED | 6.6% | 0.0% | 0.09 |
| Some college | 10.5% | 20.9% | 0.12 |
| Technical school | 3.9% | 7.0% | 0.47 |
| Associated degree | 5.3% | 11.6% | 0.21 |
| Four-year college degree | 43.4% | 41.9% | 0.87 |
| Graduate/professional degree | 28.9% | 18.6% | 0.22 |
| Income | | | |
| <$25,000 | 3.9% | 9.3% | 0.24 |
| $25,000-$50,000 | 6.6% | 11.6% | 0.34 |
| $50,000-$75,000 | 22.4% | 11.6% | 0.15 |
| $75,000-$100,000 | 18.4% | 18.6% | 0.98 |
| >$100,000 | 47.4% | 46.5% | 0.93 |
| **Child characteristics** | | | |
| Number of affected children | | | |
| One child | 94.7% | 88.4% | 0.21 |
| Two or more children | 5.3% | 11.6% | 0.21 |
| Research participation | | | |
| Clinical research | 53.3% | 65.1% | 0.22 |
| Clinical trial | 29.3% | 41.9% | 0.17 |
| Had life-threatening emergency | | | |
| Yes | 14.5% | 25.6% | 0.14 |

*Ambulatory= ability to walk independently outside for at least short distances. Note: In some cases, percents do not add to 100% because of missing values.*

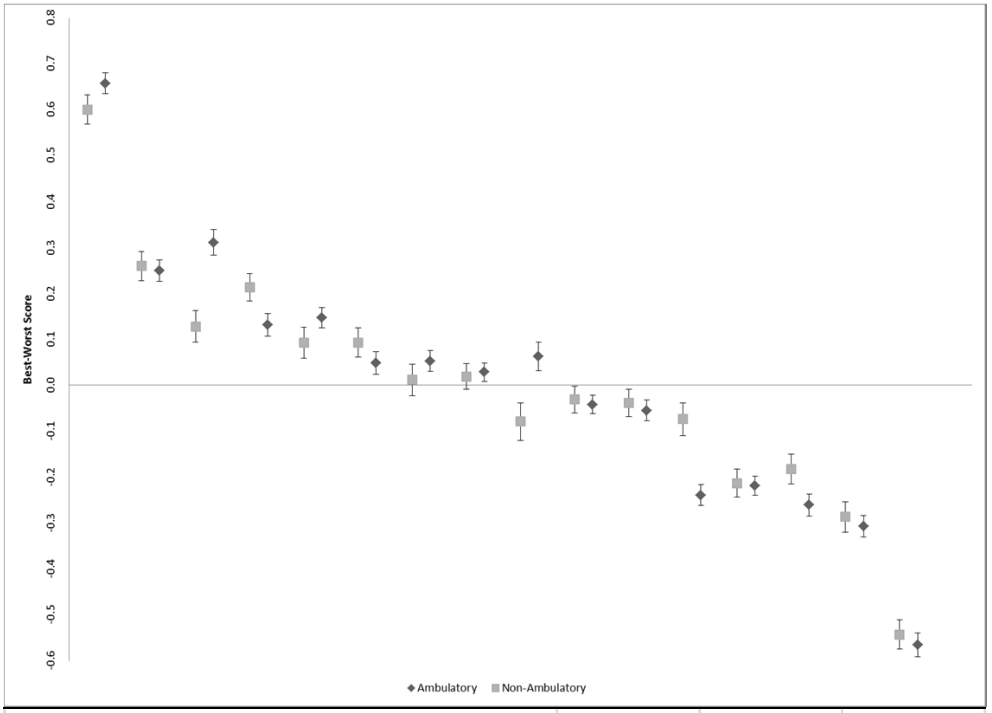
The SF-12 health status results indicate that our participants were physically healthier than the general population, with physical component scores above normative scores in 72% and at or below norm in 28%. However, 57% of participants had mental component scores (MCS) that were below the norm, 35% in the normative range, and 8% above the norm. 45 participants (40%) were identified to be at increased risk for depression compared to 20% in the normative group. The mean MCS for parents of non-ambulatory children (M=44.4, SD 11.9) was significantly higher than the mean score for parents of ambulatory children (M=39.8, SD=11.7) on independent-samples t-test, $t$ (117)= 2.05, p=0.04, two tailed.

**WORRY PRIORITIZATION**

Figure II shows the worry prioritization task's best-worst scores. In the total group, worry about "my child getting weaker" was identified as most concerning (BW score 0.64, p<0.001). Respondents also prioritized "getting the right care for my child over time" (0.25, p<0.001) and "child missing out on new treatments" (0.25, p<0.001); each of the three most prioritized items were under the "medical concerns" domain. "My child feeling happy" was the most prioritized of the child affect/emotion domain (0.16, p<0.001). "Managing my uncertainty about my child's future" was the most prioritized of the parent wellbeing domain (0.13, p<0.001). In the family and social domain, which overall was not highly prioritized compared to the other domains, "the wellbeing of my other children" was the most prioritized (-0.04, p=.01). The least prioritized items were "Having time for myself" (-0.56, p<0.001) and "Feeling isolated from other families" (-0.30, p<0.001).

Priorities for parents of ambulatory and non-ambulatory children are also shown in Figure II. Parents of ambulatory children prioritized "missing out on new treatments" significantly more than parents of non-ambulatory children, $t$ (118)= 3.34, p<0.001, two tailed. Parents of ambulatory children were also more likely to prioritize "being a good enough parent" than parents of non-ambulatory children $t$ (118)= 2.50, p=0.01, two tailed. In contrast, parents of non-ambulatory children were more likely to prioritize "child feeling like a burden on the family" than parents of ambulatory children, $t$ (118)= 3.50, p<0.001, two tailed. Finally, in comparing the rank ordering of worry items between groups, the correlation was high with a Spearman's rho of 0.90, p<0.001.

**Figure II. Worry prioritization by ambulation status**




| Attribute | Complete sample Best-worst score | P-value | 95% CI |
|---|---|---|---|
| My child getting weaker | 0.637 | 0.000 | (-0.67 , -0.60) |
| Getting the right care for my child over time | 0.254 | 0.000 | (-0.29 , -0.22) |
| My child missing out on new treatments | 0.245 | 0.000 | (-0.29 , -0.20) |
| My child feeling happy | 0.161 | 0.000 | (-0.20 , -0.12) |
| Managing my uncertainty about my child's future | 0.127 | 0.000 | (-0.16 , -0.09) |
| Afforiding care my child needs within the family bud | 0.065 | 0.000 | (-0.10 , -0.03) |
| My child having good friends | 0.038 | 0.025 | (-0.08 , 0.00) |
| My child not being able to express deep worries | 0.025 | 0.061 | (-0.06 , 0.01) |
| Being a good enough parent for my child | 0.012 | 0.319 | (-0.06 , 0.04) |
| The wellbeing of my other children | -0.038 | 0.013 | (0.00 , 0.07) |
| Me handling the emotional demands of Duchenne | -0.049 | 0.003 | (0.01 , 0.08) |
| My child feeling like a burden on the family | -0.179 | 0.000 | (0.14 , 0.22) |
| Effect of Duchenne on my closest relationships | -0.217 | 0.000 | (0.18 , 0.25) |
| My child becoming independent from me over time | -0.232 | 0.000 | (0.20 , 0.27) |

## DISCUSSION

Assessing disease impact is necessary to understand the experience of patients and caregivers, improve care provision, and inform policy. In our study describing parental DMD-related worry, respondents ranked the child's disease management as of greatest immediate worry, followed by worry about the child's affect. The impacts of DMD on the family and parents' wellbeing were less prioritized. In interpreting the results it is important to keep in mind a primary strength of Best-Worst Scaling: it allows prioritization among items that may each be valued. Thus family and parent wellbeing may be highly important, but comparatively not as important as child disease management.

Parents of non-ambulatory children had higher SF-12 MCS scores than parents of ambulatory children, which suggests adaptation to the disorder over time. Overall, the worries prioritization was similar between groups. Though both groups prioritized child medical items, the higher prioritization of worry about "missing out on new treatments" by parents of ambulatory children may reflect increased optimism for new treatment opportunities juxtaposed with a perception of a limited window during which treatment may be most effective (Peay et al. 2014b). In contrast, parents of non-ambulatory children may be resigned to fewer treatment opportunities for their children (Murray 2014) and focus more worry on their children feeling like a burden on the family as their symptoms progress.

## STUDY LIMITATIONS

There are several limitations to the study. First, the recruitment of caregivers through advocacy groups, while pragmatic and efficient, has a risk of selection bias. Second, we did not publish the preliminary, qualitative work where we identified the worry items and domains, though this has been done for other studies (for example, Ross et al., 2014) and is ideal. In addition, the domains were determined based on expert consensus and in future studies should be validated. Third, we conducted an aggregate analysis and pre-specified stratification by ambulation status, and important structures in preference heterogeneity may have been overlooked. Future research should consider a larger sample size to allow for additional stratification and segmentation analysis to adequately describe preference heterogeneity. Finally, future research should elicit DMD-related priorities from affected teenagers and adults, anticipating that DMD patients and caregivers may not agree on impact on quality of life (Usark et al. 2012).

## PRACTICE IMPLICATIONS

We found high prioritization of worries about disease management in caregivers who manage their children's DMD and make treatment decisions. Taken together with the parents' SF-12 results, the data present a parent population exhibiting negative psychosocial impact that is likely related to caring for a child with DMD. For genetics providers and other health professionals, a primary goal in assessing illness representations is to identify outcomes that are potentially alterable and inform service provision (Hale et al. 2007). Regardless of the child's disease progression, the strong prioritization of worries about weakness progression suggests that interventions that aim to reduce negative psychosocial impact on parents may be most effective when provided in conjunction with care-related interventions for the affected child.

## RESEARCH RECOMMENDATIONS

To our knowledge this study represents the first published use of BWS to prioritize among emotion-focused illness representations. Here we present a feasible, replicable community-engaged approach that demonstrates how BWS Case 1 provides an appealing alternative to quantitative rating scales. BWS Case 1 has been shown to outperform rating scales (Lee et al. 2007) and it has a particular strength in requiring participants to discriminate among items (Louvierre and Flynn 2010). It may be especially compelling for use in clinical settings because it allows estimation of preferences at an individual patient level (Louvierre and Flynn 2010), facilitating the development of clinical interventions. As we have shown, BWS benefits from a straightforward analytic approach without the need for specialized software and the results are intuitively understood. Thus BWS represents a rich, accessible analytic tool for clinicians and clinical researchers that can be used effectively across a wide range of clinical applications.

**ACKNOWLEDGEMENTS**

We appreciate the leadership and commitment of the Parent Project Muscular Dystrophy oversight committee: Pat Furlong, Brian Denger, Sharon Hesterlee, and Kathleen Kinnett. We are indebted to the stakeholder informants, parents who participated in the cognitive interviews, and caregivers who completed the survey. We acknowledge Aad Tibben's review and comments and Hadar Scharff's assistance with data cleaning and analysis of the SF-12 data.

**CONFLICT OF INTEREST**

This study was funded by Parent Project Muscular Dystrophy (PPMD). Holly Landrum Peay is an employee of PPMD and John FP Bridges was hired as a consultant by PPMD for this project. Ilene L. Hollin has no conflicts to disclose.

**HUMAN STUDIES AND INFORMED CONSENT**

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

REFERENCES

Accreditation Counsel for Genetic Counseling. (2013). Practice-Based Competencies for Genetic Counselors. Retrieved from http://www.gceducation.org/Documents/ACGC%20Core%20Competencies%20Brochure_13-Web-Revised-FINAL.pdf. Accessed December 2014.

Baines, T. & Wittkowski, A. A systematic review of the literature exploring illness perceptions in mental health utilising the self-regulation model**.** *Journal of Clinical Psychology in Medical Settings, 20(3)*, 263-274.

Black, N. (2013). Patient reported outcome measures could help transform healthcare. *British Medical Journal, 346,* f167.
Borkovec, T.D., Robinson, E., Pruzinsky, T., & Dupree, J.A. (1983). Preliminary exploration of worry: Some characteristics and processes. *Behaviour Research and Therapy*, 23, 481-482.
Boyer, F., Drame, M., Morrone, I. & Novella, J.L. (2006). Factors relating to carer burden for families of persons with muscular dystrophy. *Journal of Rehabilitation Medicine, 38(5),* 309-315.
Bridges, J.F., Hauber, A.B., Marshall, D., Lloyd, A., Prosser, L.A., Regier, D.A., Johnson, F.R. & Mauskopf, J. (2011). Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. *Value in Health,14(4),* 403-413.
Bushby, K., Finkel, R., Birnkrant, D.J., Case, L.E., Clemens, P.R., Cripe, L., Kaul, A., at al. (2010). DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurology ,9(1),* 77-93.
Creswell, J.W., Klassen, A.C., Plano Clark, V.L. & Smith, K.C. for the Office of Behavioral and Social Sciences Research. (2011). Best practices for mixed methods research in the health sciences. National Institutes of Health. Retrieved from http://obssr.od.nih.gov/mixed_methods_research. Accessed December 2014.
Daoud, A., Dooley, J.M. & Gordon, K.E. (2004). Depression in parents of children with Duchenne muscular dystrophy. *Pediatric Neurology, 31(1),* 16-19.
dosReis, S., Ng, X., Frosch, E., Reeves, G., Cunningham, C. & Bridges, J. (2015) Using best-worst scaling to measure caregiver preferences for managing their child's ADHD: A pilot study. The Patient, Epub ahead of print, doi: 10.1007/s40271-014-0098-4.
Eagle, M., Baudouin, S.V., Chandler, C., Giddings, D.R., Bullock, R. & Bushby, K. (2002). Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders,12(10),* 926-929.
Erdem, S. & Rigby, D. (2013). Investigating heterogeneity in the characterization of risks using best worst scaling. *Risk Analysis*, *33(9),* 1728-1748.
Flanigan, KM. (2014). Duchenne and Becker muscular dystrophies. *Neurologic Clin*ics *32(3),* 671-688.
Flynn, T. N., Louviere, J. J., Peters, T. J., & Coast, J. (2007). Best worst scaling: what it can do for health care research and how to do it. *Journal of Health Economics, 26(1),* 171-89.
Flynn, T.N. (2010). Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. *Expert Review of Pharmacoeconomics & Outcomes*

*Research, 10(3),* 259-267.
Gallego, G., Bridges, J.F., Flynn, T., Blauvelt, B.M. & Niessen, L.W. (2012). Using best-worst scaling in horizon scanning for hepatocellular carcinoma technologies. *International Journal of Technology Assessment in Health Care, 28(3),* 339-346.
Grewal, I., Lewis, J., Flynn, T., Brown, J., Bond, J. & Coast, J. (2006). Developing attributes for a generic quality of life measure for older people: preferences or capabilities? *Social Science in Medicine, 62(8),* 1891-1901.
Johnson, F.R., Hauber, A.B., & Poulos, C.M. (2009). A brief introduction to the use of stated-choice methods to measure preferences for treatment benefits and risks. RTI Press publication No. RR-0009-0909. Research Triangle Park, NC: RTI International. Retrieved from http://www.rti.org/rtipress. Accessed December 2014.
Hale, E.D., Treharne, G.J. & Kitas, G.D. (2007). The Common-Sense Model of self-regulation of health and illness: how can we use it to understand and respond to our patients' needs? *Rheumatology, 46,* 904–906.
Hatzmann, J., Heymans, H.S., Ferrer-i-Carbonell, A., van Praag, B.M. & Grootenhuis, M.A. (2008). Hidden consequences of success in pediatrics: parental health-related quality of life—results from the Care Project. *Pediatrics, 122(5),* e1030-1038.
Haywood K.L. (2006). Patient-reported outcome I: measuring what matters in musculoskeletal care. *Musculoskeletal Care, 4(4),* 187-203.
Hollin, I.L., Peay, H.L. & Bridges, J.F. (2014). Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of Best-Worst Scaling and Conjoint Analysis. *The Patient, Dec 19*. Epub ahead of print.
Kenneson, A. & Bobo, J.K. (2010). The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. *Health & Social Care in the Community, 18(5),* 520-528.
Landfeldt, E., Lindgren, P., Bell, C.F., Schmitt, C., Guglieri, M., Straub, V., Lochmüller, H. & Bushby, K. (2014). The burden of Duchenne muscular dystrophy: An international, cross-sectional study. *Neurology, 83(6),* 529-536.
Lee, J.A., Soutar, G. & Louviere, J.J. (2007). Measuring values using best worst scaling: the LOV example. *Psychology & Marketing, 24 (12),* 1043-1058.
Louviere, J.J. & Flynn, T.N. (2001). Using best- worst scaling choice experiments to measure public perceptions and preferences for healthcare reform in Australia. *The Patient, 3,* 275–283.
Louviere, J.J., & Islam T. (2008). A comparison of importance weights and willingness-to-pay measures derived from choice-based conjoint, constant sum scales and best–worst scaling.

*Journal of Business Research, 61(9*), 903-911.
Magnan, R.E., Köblitz, A.R., Zielke, D.J. & McCaul, K.D. (2009). The effects of warning smokers on perceived risk, worry, and motivation to quit. *Annals of Behavioral Medicine, 37(1),* 46-57.
McAndrew, L.M., Mora, P.A., Quigley, K.S., Leventhal, E.A. & Leventhal. H. (2014). Using the common sense model of self-regulation to understand the relationship between symptom reporting and trait negative affect. *International Journal of Behavioral Medicine, 21(6),* 989-994.
McAndrew, L.M., Musumeci-Szabo, T.J., Mora, P.A., Vileikyte, L., Burns, E., Halm, E.A., Leventhal, E.A. & Leventhal, H. (2008). Using the common sense model to design interventions for the prevention and management of chronic illness threats: from description to process. *British Journal of Health Psychology, 13(2),* 195**–**204.
McCaul, KD & Goetz, P.W. (2008). Worry. *Health Behavior Constructs: Theory, Measurement & Research,* National Cancer Institute. Retrieved from http://cancercontrol.cancer.gov/brp/constructs/worry/index.html. Accessed December 2014.
Molassiotis, A., Emsley, R., Ashcroft, D., Caress, A., Ellis, J., Wagland, R., Bailey, C.D., at al. (2012). Applying Best-Worst scaling methodology to establish delivery preferences of a symptom supportive care intervention in patients with lung cancer. *Lung Cancer, 77(1),* 199-204.
Murray, L. (2014). Left out in the cold: Barriers to clinical trial participation and the impact on parents of sons with Duchenne muscular dystrophy. Published Abstract, National Society of Genetic Counselors Annual Conference, Presented September 20, 2014.
Optum SF-12v2 Health Survey: Advantages of Norm-Based Scoring. (n.d.) Retrieved from https://www.optum.com/content/dam/optum/resources/Manual%20Excerpts/Norm-based%20Scoring%20(NBS).pdf. Accessed December 2014.
Pangalila, R.F., van den Bos, G.A., Stam, H.J., van Exel, N.J., Brouwer, W.B. & Roebroeck, M.E. (2012). Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. *Disability and Rehabilitation, 34(12),* 988-996.
Peay, H.L., Hollin, I., Fischer, R. & Bridges, J.F. (2014a). A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. *Clinical Therapeutics, 36(5),* 624-637.
Peay, H.L., Tibben, A., Fisher, T., Brenna, E. & Biesecker, B.B. (2014b). Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. *Clinical Trials, 11(1),* 77-85.
Politi M.C. & Street R.L. (2011). The importance of communication in collaborative decision

making: facilitating shared mind and the management of uncertainty. *Journal of evaluation in clinical practice,17(4),* 579-584.

Razafsha, M., Behforuzi, H., Azari. H., Zhang, Z., Wang, K.K., Kobeissy, F.H. & Gold, M.S. (2010). Qualitative versus quantitative methods in psychiatric research. *Methods in Molecular Biology, 829*, 49-62.

Reid, D.T. & Renwick, R.M. (2001). Relating familial stress to the psychosocial adjustment of adolescents with Duchenne muscular dystrophy. *International Journal of Rehabilitation Research, 24(2),* 83-93.

Ross, M., Bridges, J., Ng, X., Wagner, L., Frosch, E., Reeves, G. & dosReis. S. (2015) A best-worst scaling experiment to prioritize caregiver concerns with attention deficit/hyperactivity disorder (ADHD) medicine for children, *Psychiatric Services*, Epub ahead of print, doi: 10.1176/appi.ps.201300525.

U.S. Food and Drug Administration (FDA). (n.d.) Enhancing benefit-risk assessment in regulatory decision-making. Retrieved from http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm326192.htm. Accessed March 2014.

Uzark, K., King, E., Cripe, L., Spicer, R., Sage, J., Kinnett, K., Wong, B., et al. (2012). Health-related quality of life in children and adolescents With Duchenne muscular dystrophy. *Pediatrics,130,* 1–8.

Ware, J.E., Kosinski, M. & Keller, S.D. (1996). A 12 Item Short Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care, 34,* 220-233.

# 6

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

CLINICAL TRIALS ARTICLE Clinical Trials 2013; 0: 1–9

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

Holly L Peay[a,b], Aad Tibben[b], Tyler Fisher[a], Ethan Brenna[a] and Barbara B Biesecker[a]

***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

[a]Social and Behavioral Research Branch, National Human Genome Research Institute, Bethesda, MD, USA, [b]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands
**Author for correspondence:** Holly L Peay, Social and Behavioral Research Branch, National Human Genome Research Institute, Building 31, Room B1B36, 31 Center Drive MSC 2073, Bethesda, MD 20892, USA.
Email: hpeay@mail.nih.gov


10.1177/1740774513512726

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 $\geq$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 knowledgably 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

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 nonsuccessful 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.

## Acknowledgments

We thank the parents and clinical investigators who were willing to share their perceptions and experiences.

## Funding

This work was supported by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health.

## 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.

## References

1. **McCann SK, Campbell MK, Entwistle VA.** Reasons for participating in randomised controlled trials: Conditional altruism and considerations for self. *Trials* 2010; **11**: 31.
2. **Kost RG, Lee LM, Yessis J, *et al*.** Assessing research participants' perceptions of their clinical research experiences. *Clin Transl Sci* 2011; **4**: 403–13.
3. **Christopher PP, Leykin Y, Appelbaum PS, *et al*.** Enrolling in deep brain stimulation research for depression:

Influences on potential subjects' decision making. *Depress Anxiety* 2012; **29**: 139–46.
4. **Carroll R**, **Antigua J**, **Taichman D**, *et al*. Motivations of patients with pulmonary arterial hypertension to participate in randomized clinical trials. *Clin Trials* 2012; **9**: 348–57.
5. **Nickel PJ**. Vulnerable populations in research: The case of the seriously ill. *Theor Med Bioeth* 2006; **27**: 245–64.
6. **Annas GJ**. Questing for grails: Duplicity, betrayal and self-deception in postmodern medical research. *J Contemp Health Law Policy* 1996; **12**: 297–324.
7. **Henderson GE**, **Churchill LR**, **Davis AM**, *et al*. Clinical trials and medical care: Defining the therapeutic misconception. *PLoS Med* 2007; **4**: e324.
8. **Shilling V**, **Young B**. How do parents experience being asked to enter a child in a randomised controlled trial? *BMC Med Ethics* 2009; **10**: 1.
9. **Horng S**, **Grady C**. Misunderstanding in clinical research: Distinguishing therapeutic misconception, therapeutic misestimation, and therapeutic optimism. *IRB* 2003; **25**: 11–16.
10. **Jansen LA**. Two concepts of therapeutic optimism. *J Med Ethics* 2011; **37**: 563–66.
11. **De Vries MC**, **Houtlosser M**, **Wit JM**, *et al*. Ethical issues at the interface of clinical care and research practice in pediatric oncology: A narrative review of parents' and physicians' experiences. *BMC Med Ethics* 2011; **12**: 18.
12. **Yanos PT**, **Ziedonis DM**. The patient-oriented clinician-researcher: Advantages and challenges of being a double agent. *Psychiatr Serv* 2006; **57**: 249–53.
13. **Davis AM**, **Hull SC**, **Grady C**, *et al*. The invisible hand in clinical research: The study coordinator's critical role in human subjects protection. *J Law Med Ethics* 2002; **30**: 411–19.
14. **Bernstein M**. Conflict of interest: It is ethical for an investigator to also be the primary care-giver in a clinical trial. *J Neurooncol* 2003; **63**(2): 107–08.
15. **Miller FG**, **Rosenstein DL**. The therapeutic orientation to clinical trials. *N Engl J Med* 2003; **348**: 1383–86.
16. **Garralda ME**, **McConachie H**, **Le Couteur A**, *et al*. Emotional impact of genetic trials in progressive paediatric disorders: A dose-ranging exon-skipping trial in Duchenne muscular dystrophy. *Child Care Health Dev* 2012; **39**: 449–55.
17. **Peltz SW**, **Morsy M**, **Welch EM**, **Jacobson A**. Ataluren as an agent for therapeutic nonsense suppression. *Annu Rev Med* 2013; **64**: 407–25.
18. **Terry SF**, **Terry PF**, **Rauen KA**, *et al*. Advocacy groups as research organizations: The PXE International example. *Nat Rev Genet* 2007; **8**: 157–64.
19. **Dresser R**. Patient advocates in research: New possibilities, new problems. *Wash Univ J Law Pol* 2003; **11**: 237–48.
20. **Cohen PD**, **Herman L**, **Jedlinski S**, *et al*. Ethical issues in clinical neuroscience research: A patient's perspective. *Neurotherapeutics* 2007; **4**: 537–44.
21. **Woods S**, **Hagger LE**, **McCormack P**. Therapeutic misconception: Hope, trust and misconception in paediatric research. *Health Care Anal* 2012; doi: 10.1007/s10728-012-0201-8 (Epub ahead of print).
22. **Jansen LA**, **Appelbaum PS**, **Klein WM**, *et al*. Unrealistic optimism in early-phase oncology trials. *IRB* 2011; **33**: 1–8.

# 7

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

**CHAPTER 7.**

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

Authors:
Holly L. Peay, MS, Parent Project Muscular Dystrophy; Leiden University Medical Centre
Hadar Scharff, MPH, Parent Project Muscular Dystrophy
Aad Tibben, PhD, Center for Human and Clinical Genetics, Leiden University Medical Centre
Benjamin Wilfond, MD, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute
Janice Bowie, PhD, MPH, Department of Health, Behavior & Society, Johns Hopkins Bloomberg School of Public Health
Joanna Johnson, MEd, Parent Advocate, Parent Project Muscular Dystrophy
Kanneboyina Nagaraju, PhD, DVM, Children's National Medical Center
Diana Escolar, MD, Kennedy Krieger Institute, The Johns Hopkins School of Medicine
Jonathan Piacentino, Self Advocate, Parent Project Muscular Dystrophy
Barbara B. Biesecker, PhD, MS, Social and Behavioral Research Branch, National Human Genome Research Institute

**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 study[9] 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 King[17] 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 recommendations[17] 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 trail 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.

**ACKNOWLEDGMENTS**

We are indebted to the study participants for sharing their experiences. Benjamin Cumbo, a self-advocate, participated as a CBPR advisor for the first half of the project. Kathryn Porter, JD, MPH provided manuscript input and support. The project described was supported by Grant Number R21NS077286 from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years – four states, 2007. MMWR Morb Wkly Rep 2009; 58(40):1119-1122.
2. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C, DMD Care Considerations Working Group: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010; 9(1): 77-93.
3. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K: Survival in duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord 2002; 12(10): 926-929.

4. Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V, Lochmüller H, Bushby K: The burden of Duchenne muscular dystrophy: An international, cross-sectional study. Neurology 2014; 83(6):529-36.
5. Kenneson A, Bobo JK: The effect of caregiving on women in families with Duchenne/Becker muscular dystrophy. Health Soc Care Community 2010; 18(5):520-528.
6. Ouyang L, Grosse SD, Fox MH, Bolen J: A national profile of health care and family impacts of children with muscular dystrophy and special health care needs in the United States. J Child Neurol 2012; 27:569-576.
7. Ouyang L, Grosse SD, Kenneson A: Health care utilization and expenditures for children and young adults with muscular dystrophy in a privately insured population. J Child Neurol 2008; 23:883-888.
8. Aartsma-Rus A, Van Ommen GJ, Kaplan JC: Innovating therapies for muscle diseases. Handb Clin Neurol. 2013;113:1497-1501.
9. Peay HL, Tibben A, Fisher T, Brenna E, Biesecker BB: Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. Clin Trials 2014; 11(1):77-85.
10. Samson A, Tomiak E, Dimillo J, Lavigne R, Miles S, Choquette M, Chakraborty P, Jacob P: The lived experience of hope among parents of a child with Duchenne muscular dystrophy: perceiving the human being beyond the illness. Chronic Illn 2009; 5(2):103-114.
11. Erby LH, Rushton C, Geller G: “My son is still walking”: stages of receptivity to discussions of advance care planning among parents of sons with Duchenne muscular dystrophy. Semin Pediatr Neurol 2006; 13(2):132-140.
12. Caldwell PHY, Butow PN, Craig JC: Parents’ attitudes to children’s participation in randomized controlled trials. J Pediatr 2003; 142:554-559.
13. Rothmier JD, Lasley MV, Shapiro GG: Factors influencing parental consent in pediatric clinical research. Pediatrics 2003; 111(5):1037-1041.
14. Perez ME, Langseder A, Lazar E, Youssef NN: Parental perceptions of research after completion of placebo-controlled trials in pediatric gastroenterology. J Pediatr Gastroenterol Nutr. 2010; 51(3):309-313.
15. Tierney E, Aman M, Stout D, Pappas K, Arnold LE, Vitiello B, Scahill L, McDougle C, McCracken J, Wheeler C, Martin A, Posey D, Shah B: Parent satisfaction in a multi-site

acute trial of risperidone in children with autism: a social validity study. Psychopharmacology (Berl) 2007; 191:149-157.

16. Israel BA, Schulz AJ, Parker EA, Becker AB: Community-Campus Partnerships for Health. Community-based participatory research: policy recommendations for promoting a partnership approach in health research. Educ Health 2001; 14(2):182-197.
17. King NM: Defining and describing benefit appropriately in clinical trials. J Law, Med Ethics 28 2000; 28(4) 332-343.

8

# 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**

Authors:
Holly L Peay, MS, Parent Project Muscular Dystrophy; Leiden University Medical Centre
Hadar Scharff, MPH, Parent Project Muscular Dystrophy
Aad Tibben, PhD, Department of Clinical Genetics, Leiden University Medical Centre
Benjamin Wilfond, MD, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute
Janice Bowie, PhD, MPH, Department of Health, Behavior & Society, Johns Hopkins Bloomberg School of Public Health
Joanna Johnson, MEd, Parent Advocate, Parent Project Muscular Dystrophy
Kanneboyina Nagaraju, PhD, DVM, Children's National Medical Center
Diana Escolar, MD, Kennedy Krieger Institute, The Johns Hopkins School of Medicine
Jonathan Piacentino, Self Advocate, Parent Project Muscular Dystrophy
Barbara B Biesecker, PhD, MS, Social and Behavioral Research Branch, National Human Genome Research Institute

The study was supported by Grant Number R21NS077286 from the National Institute of Neurological Disorders and Stroke.

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

**ACKNOWLEDGEMENTS**

We are indebted to the study participants for sharing their experiences. Benjamin Cumbo, a self-advocate, participated as a CBPR advisor for the first half of the project. Kathryn Porter, JD, MPH contributed to editing the manuscript. The project described was supported by Grant Number R21NS077286 from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

REFERENCES


1. Daugherty, C.K. (1999) Impact of therapeutic research on informed consent and the ethics of clinical trials: a medical oncology perspective. J Clin Oncol, 17(5): 1601-1617.
2. ECRI evidence report. Patients' reasons for participation in clinical trials and effect of trial participation on patient outcomes. Available at: https://www.ecri.org/Documents/Clinical_Trials_Patient_Guide_Evidence_Report.pdf. Accessed 10 July 2014.
3. Elwyn G and Miron-Shatz T. (2009) Deliberation before determination: the definition and evaluation of good decision making. Health Expectations, 13, pp.139–147.
4. Caldwell, P.H.Y., Butow, P.N. and Craig, J.C. (2003) Parents' attitudes to children's participation in randomized controlled trials. J Pediatr, 142: 554-559.
5. Rothmier, J.D, Lasley, M.V. and Shapiro, G.G. (2003) Factors influencing parental consent in pediatric clinical research. Pediatrics,111(5): 1037-1041.
6. Peay, H.L, Tibben, A., Fisher, T., Brenna, E. and Biesecker, B.B. (2104) Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. Clin Trials,11(1): 77-85.
7. Bushby, K., Finkel, R., Birnkrant, D.J., Case, L.E., Clemens, P.R., Cripe, L., Kaul, A., Kinnett, K., McDonald, C., Pandya, S., Poysky, J., Shapiro, F., Tomezsko, J. and Constantin, C. (2010) DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol,9(1): 77-93.
8. Eagle, M., Baudouin, S.V., Chandler, C., Giddings, D.R., Bullock, R.and Bushby, K. (2002) Survival in duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord,12(10): 926-929.
9. Aartsma-Rus A, Van Ommen GJ, Kaplan JC. Innovating therapies for muscle diseases. Handb Clin Neurol, 2013;113:1497-501.
10. Israel, B.A., Schulz A.J., Parker E.A. and Becker, A.B. (2001) Community-based participatory research: policy recommendations for promoting a partnership approach in health research. Education for Health,14(2): 182-197.
11. Marteau, T.M., Dormandy, E. and Michie, S. (2001) A measure of informed choice. Health Expect, 4(2): 99-108.

12. Allen, K.A. (2014) Parental decision-making for medically complex infants and children: An integrated literature review. Int J Nurs Stud, 51(9): 1289-1304.
13. Peay, H.L., Hollin, I., Fischer, R. and Bridges, J.F. (2014) A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. Clin Ther, 36(5): 624-637.
14. Jansen, L.A. (2014) Mindsets, informed consent, and research. Hastings Center Report, 44(1): 25-32.
15. Parent Project Muscular Dystrophy. Putting patients first: recommendations to speed responsible access to new therapies for Duchenne muscular dystrophy and other rare, serious and life-threatening neurologic disorders. Available at: http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_patients#sthash.ABG4EREB.dpuf. Accessed 22 July 2014.
16. Sasinowski, F.J. Quantum of effectiveness evidence in FDA's approval of orphan drugs: cataloguing FDA's flexibility in regulating therapies for persons with rare disorders. Available at http://www.rarediseases.org/docs/policy/NORDstudyofFDAapprovaloforphandrugs.pdf. Accessed 22 July 2014.
17. Field, M.J. and Boat, T.F., editors. (2010) Rare diseases and orphan products: accelerating research and development. Washington, DC. National Academies Press.
18. Henderson, G.E. (2011) Is informed consent broken? Am J Med Sci, 342(4): 267-272.

# 9

# Discussion, Summary and Implications

# Conclusions

## CHAPTER 9.
## Summary, Discussion and Implications

This thesis presents a series of translational research studies. They employ a diverse set of research methods to explore topics of importance to a patient community. In this section we summarize the outcomes and implications of each study, after which the community-engaged research (CEnR) approaches employed in the studies are rated and reviewed.

A common limitation shared by all of the studies was the use of PPMD and the DuchenneConnect self-report registry for recruitment. Families who opt into participating in a disease advocacy organization or a self-report registry, and who then opt to participate in a social science study, may not be representative of families managing Duchenne and Becker muscular dystrophies. Future research would benefit from additional consecutive in-clinic recruitment to improve the range of perspectives that are included in qualitative research and to ensure generalizable quantitative research.

### Advocacy and programmatic implications

The overarching objective of the studies was to inform PPMD's interventions and/or policy and advocacy approaches. Though the impact varied, all were successful in that objective. Achieving the objective was facilitated through the use of a range of community engagement approaches.

**Mothers' wellbeing studies** (Chapter 2) provided clinically-relevant data about mothers' unmet support needs and adaptation to caregiving for a child with DBMD. The pragmatic and positive focus of the study aims and instruments reflected stakeholders' attitudes that caring for a child with DBMD comes with benefits, and clinical interventions should highlight strengths and wellbeing rather than burden and deficit.

Mothers identified many areas of resilience and support. We identified a need to improve use of respite care. Findings also showed that the least-met support needs are related to coping with challenging emotions associated with DBMD. Predictors of psychological adaptation included greater resilience and endorsement of positive impact of DBMD on the family. Though existing literature places emphasis on burden of illness, we found that perceived burden did not predict adaptation.

Study results include unexpected findings about mother's age, child's disease progression, psychosocial support needs, and adaptation. We found opposite effects of mother's age (with younger age predictive of higher adaptation scores) and child's functional status (with worse functional status associated with, but not an independent predictor of, higher adaptation scores) on mothers' psychological adaptation. The results suggest that while mothers may be able to attribute more benefit to the DBMD experience and perceive lower unmet needs as their children's symptoms become more advanced, their resilience may be challenged as they age. Additional exploration is needed to better understand the effects of increasing mother's age and worsening child's functional status on psychosocial needs, care facilitators, and psychological adaptation.

Clinical implications from the study on mothers' wellbeing include the need for systematic exploration of caregivers' unmet support needs, especially those related to coping with DMD-related uncertainty and fear. Efforts to improve mothers' adaptation should focus on fostering resilience and enhancing benefit finding through identification of positive aspects of living with DBDM. Clinicians may be able to identify specific caregiving needs and customize interventions based on the use of simple, targeted questions similar to the questions used in this study.

Summaries of the research findings have been shared through Parent Project Muscular Dystrophy forums, including social media and the PPMD annual conference. Data presented in this thesis informed a wellness intervention at PPMD's annual conference in 2013 and was used to support two grant proposals on caregivers' wellbeing. In late 2014 we initiated a carrier mothers' program guided by the study results through DuchenneConnect, a longitudinal patient and caregiver self-report registry. In addition, the longitudinal mothers' wellbeing study is ongoing. To extend the results from the first two years of data collection, the third year's survey included measures on uncertainty, spirituality, and hope.

In the **treatment preferences and impact study** (Chapters 3-5), using Best-Worst Scaling methodology we found that caregivers were willing to accept increased risk for a serious or fatal outcome when balanced with a non-curative treatment, even absent lifespan improvement. The addition of a simple conjoint analysis as a second stated preferences method validated the major findings and provided important, policy-relevant information about intention to use specific therapies. In the worry study we successfully differentiated among a set of highly relevant

worries, concluding that the most pressing concerns entailed worries about symptom progression and access to medical care, followed by the child being happy. Worries related to parents' wellbeing and family and social impact were relatively less prioritized. Best-Worst Scaling represents a compelling method to explore and quantify disease perceptions and impact that is rarely used in health-related social science studies.

Of the studies presented in this thesis, the treatment preferences study had the most remarkable advocacy and policy impact. We described a model process for advocacy organizations aiming to promote patient-centered drug development. Study results were distributed to the U.S. Food and Drug Administration (FDA) personnel at several in-person forums to inform their assessment of emerging DMD therapies. The study has been cited by FDA personnel, who identified it as a replicable template for other advocacy organizations to follow[1] and stressed the need for such research to be conducted by other organizations.[2] Several biopharmaceutical companies have used or plan to use the data from this study in their regulatory processes. The study was also cited in the U.S. House of Representatives Energy and Commerce Committee 21st Century Cures Initiative and described in a Committee hearing.[3]

The study results provided PPMD with a compelling message for FDA engagement. This led the FDA to urge PPMD to develop draft guidance for DMD—a first for a rare-disease advocacy group. It was submitted to the FDA on June 2014. The guidance begins with a chapter on benefit/risk assessment, which includes a summary of the results and advises sponsors to measure patient/caregiver preferences as part of their drug development and regulatory submission processes.[4]

Since completing the study, the authors have presented the results at more than 20 professional and advocacy venues. Almost a dozen advocacy organizations in other disease areas have indicated their intent to use it as a model. As a representation of ongoing impact, in November 2014 PPMD announced a collaboration with Santhera Pharmaceuticals to develop a new benefit/risk study focused on pulmonary therapies for Duchenne.[5]

**Decision making in clinical trials** (Chapters 7-8) is an area of considerable interest for clinical trial sponsors, clinical trial site teams, institutional review boards, and advocacy organizations. Our studies highlighted the complexity of clinical trial decision making, especially in the context

of a rare, progressive pediatric disorder, where our parent participants equated doing “nothing” (i.e., not participating in a trial) with doing harm. Parents’ decisions were strongly influenced by the chance for individual benefit to their children, but the participants did not display classically-defined therapeutic misconception. The adaptive optimism engendered by the availability of trial participation was another anticipated benefit—and one that was highly valued by both parents and clinicians on clinical trial teams. Parents reported undertaking a benefit-risk assessment and developing intentions to participate in clinical trials before the informed consent process.

Clinicians described more influence on parental decisions than attributed by parents. They reported feeling responsible to facilitate informed decisions while maintaining parents’ optimism. Based on the findings we suggest that clinicians, sponsors, and advocacy organizations develop approaches to engage families in anticipatory guidance about potential negative trial outcomes, anticipating that these efforts may assist clinicians in having balanced discussions with families while providing some protection against decisional regret.

We also provide a report of how parents assessed and valued perceived benefits during clinical trial participation, which has implications for their continued investment in the trial. Participants described a complex, dynamic process of defining, evaluating, and assessing “net benefit” as an ongoing coping process. Most perceived individual benefits to their children, as well as other benefits that included altruism, close relationships with the research team, and enhanced optimism.

Results from both interview studies informed the development of a quantitative survey about clinical trial decision making, for which recruitment has recently closed. To inform future research, we are in process of using the qualitative and quantitative results to adapt Leventhal’s common-sense model of self-regulation, which describes responses to and management of health threats[6]. The revised model will propose that decisions about disease management include expectations and hopes as cognitive and emotional appraisals that inform parallel cognitive and emotional processing. This will provide a framework to assess decision making influences and processes in the clinical trial context. We next plan to develop and evaluate a decision aid that focuses on identifying and distinguishing between clinical trial expectations and optimistic hopes.

Data from these studies have been presented to clinical trials sponsors in group and individual settings; to relevant organizations such as the Patient Centered Outcomes Research Institute and through the Clinical and Translational Science Award (CTSA) program; to clinician investigators at the World Muscle Society and other professional forums; and to patients and families through PPMD forums. The data have been used to inform the development of new educational content for patients and families and to justify sessions on trial expectations at the PPMD annual conference. Finally, themes from the study have been integrated into research exploring clinical trial decision making in other disease communities (spinal muscular atrophy, fragile X syndrome and HIV).

**Implications for Community-Engaged Research Approaches**

Table 2 presents a rating of the approaches used in this thesis on the CEnR continuum. We found that community engagement at level 1 or higher on the continuum is important to posing and answering questions of importance. The utility and feasibility of higher levels of community engagement varied based on the program's timeline, budget and needs. The community-based participatory research (CBPR) approach we used in the clinical trial study was extremely beneficial, but required a supporting timeline and budget that may not always be feasible. In the treatment preference study, the researchers and advisory team chose to target community engagement around communicating about the need for, and implications of, the study and for identifying the attributes and levels used in the instrument. We found that 'hybrid' community engagement approaches were natural for research conducted within an advocacy organization, and took advantage of PPMD's community reach and respect.

**Table 2. Rating of Community-Engaged Research Approaches**

| Study | Mothers' Wellbeing Study | Duchenne Treatment Preferences | Clinical Trial Expectations Pilot | Clinical Trial Expectations and Experiences |
|---|---|---|---|---|
| **A. Inclusion of stakeholders in research program development** | Level 3 | Level 2 (+ significant input, item development) | Level 1 | Level 3 |
| **B. Inclusion of stakeholders in decision making** | Level 2 | Level 2 | Level 1 | Level 3 |
| **C. Increasing stakeholders' research advisory capacity** | Level 2 | Level 2 | Level 1 | Level 3 |
| **D. Disseminating study information** | Level 3 | Level 3 | Level 1 (+ lay summary) | Level 3 |
| **E. Developing accountable policy, service & intervention recommendations** | Level 2 | Level 3 | Level 2 | Level 3 |

**Lessons on Community Engagement**

Following are some of the important lessons we learned about community engagement.

- In the mothers' welling study, our engagement efforts highlighted the importance of framing the disease experience. Findings underscore the need to re-orient negative predictor and outcome variables used in traditional disease impact studies to positive predictor and outcome variables that are focused on wellbeing.
- In the treatment preferences study, the importance of researcher flexibility when faced with stakeholders' responses to engagement efforts was recognized. Even with

engagement, not everyone in the community was in agreement about the value of providing quantified data to regulators. Thus, we added a complimentary approach (PPMD's "Share your Story" outreach, which resulted in an FDA-focused resource called "Patients are Waiting"[7]) to increase community acceptance and demonstrate our appreciation for the power of patient and family testimony.

- The clinical trials studies highlighted the benefits of a highly-engaged CBPR approach for addressing complex ethical issues with implications for a wide range of stakeholders. Incorporating a wide range of experienced stakeholders in the process helped to frame ethical challenges in an acceptable way and suggested future research and interventions that should be satisfactory to the community.

The community engagement undertaken in these studies had an important, and sometimes dramatic, impact on the study objectives, aims, design, analysis, interpretation, and dissemination. There is likely not a one-size-fits-all approach to community engagement. Instead, engagement must be done meaningfully so stakeholders have a real chance to understand and influence the research agenda. Long-term engagement requires education and support to expand parents' and caregivers' research imaginations, so they can be active participants in setting a research agenda. Researchers must be open to change and appreciate that their perspectives and research experiences will expand and grow as a benefit of the engagement.

REFERENCES


1. Food and Drug Administration "Complex Issues in Rare Disease Drug Development" public workshop, Jan 7 2014, Maryland USA
2. The Pink Sheet. "Woodcock Encourages Patient Groups To Take Lead To Speed Regulatory Process, Development." July 11 2014 Available at https://www.pharmamedtechbi.com/publications/the-pink-sheet-daily?issue=Jul-11-2014
3. Testimony of Pat Furlong Parent Project Muscular Dystrophy, Committee on Energy & Commerce Subcommittee on Health July 11, 2014 available at http://democrats.energycommerce.house.gov/sites/default/files/documents/Testimony-Furlong-HE-21st-Century-Cures-Incorporating-Patient-Perspective-2014-7-11.pdf
4. Parent Project Muscular Dystrophy, "FDA Draft Guidance on Duchenne" 2014. Available

at http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance

5. Parent Project Muscular Dystrophy, “PPMD and Santhera Pharmaceuticals Team Up on New Benefit/Risk Study Focused on Pulmonary Therapies” 2014. Available at http://community.parentprojectmd.org/profiles/blogs/ppmd-and-santhera-pharmaceuticals-team-up-on-new-benefit-risk
6. Leventhal, H., Nerenz, D. R., & Steele, D. J. (1984). Illness representations and coping with health threats. In A. Baum, S. E. Taylor, & D. J. Singer (Eds.), Handbook of psychology and health: Social psychological aspects of health (Vol. 4, pp. 219–252). Hillsdale, NJ: Erlbaum.
7. Parent Project Muscular Dystrophy. “Patients are Waiting” 2014. Available at http://www.parentprojectmd.org/site/DocServer/SYS.pdf?docID=15643

# Samenvatting en discussie

***Samenvatting, Discussie en Implicaties***

In dit proefschrift worden een aantal translationele studies beschreven waarin onderzoeksmethoden worden gebruikt die van belang zijn voor patiënten met Duchenne/Becker spierdystrofie (DBMD) en hun verzorgers (stakeholders). In dit hoofdstuk worden de bevindingen en implicaties samengevat. Ten slotte wordt besproken op welke wijze de inbreng van DBMD patiënten, families, en andere stakeholders in deze studies kan worden gerealiseerd.

Een beperking van alle in dit proefschrift beschreven studies was dat deelnemers aan de studies werden geworven via het PPMD (Parent Project Muscular Dystrophy) en de DuchenneConnect self-report registry. Families die lid zijn van een patiënten organisatie of Vereniging en die deelnemen aan een sociaal-wetenschappelijk onderzoek zijn mogelijk niet representatief voor de totale Duchenne/ Becker gemeenschap. Toekomstig onderzoek kan baat hebben bij werving via de (poli-)klinieken, waarmee een breder beeld kan worden gevormd en de generaliseerbaarheid van de bevindingen groter is.

**Advocacy and Programmatische Implicaties**
Het overkoepelende doel van deze studies was het richting geven aan en het ondersteunen van het beleid van de PPMD en patiëntenorganisaties. Geconcludeerd kan worden dat elke studie hieraan een belangrijke bijdrage heeft geleverd. Het doel kon worden bereikt door de actieve betrokkenheid van DBMD patiënten, families, en andere stakeholders.

**Het welzijn van moeders** (Hoofdstuk 2). In deze studie werden de psychosociale behoeften van moeders van een of meerdere kinderen met Duchenne/Becker spierdystrofie onderzocht. Specifiek werd gekeken naar de behoefte aan rust en ontspanning, het vermogen om zorg te verlenen, en de mate van aanpassing met betrekking tot de zorg voor een kind met DBMD. De positieve focus van het doel van de studie en de gebruikte vragenlijsten weerspiegelden de instelling van de deelnemende moeders: zorgen voor een kind met DBMD heeft ook zijn positieve kanten en klinische interventies moeten zich meer richten op de kracht en welzijn van

moeders dan op de last die de ziekte met zich mee brengt en gevoelens van onvermogen om zorg te bieden.

Wij vonden bij de moeders diverse vormen van zorgkracht, vooral op het gebied van sociale steun. Moeders hebben een grote behoefte aan momenten van rust, en aan tijdelijk ontlast te worden van zorg. Moeders ervoeren vooral dat geen gehoor wordt gegeven aan hoe zij met emoties over DBMD moeten omgaan. Voorspellers voor psychologische aanpassing waren onder meer grotere veerkracht en bevestiging van de positieve impact van DBMD op het gezin. Hoewel de huidige literatuur vooral de nadruk legt op de last van de ziekte, vonden wij dat de perceptie van de last van de ziekte niet voorspellend was voor de mate van aanpassing.

Het onderzoek toonde enkele onverwachte bevindingen met betrekking tot de leeftijd van moeders, het beloop van de ziekte, psychosociale steun, en psychologische aanpassing. In de longitudinale studie vonden wij tegengestelde effecten van de leeftijd van moeders (jongere leeftijd voorspelde betere adaptatie) en de functionele conditie van het DBMD-kind (slechtere conditie voorspelde betere adaptatie) op de psychologische adaptatie. De resultaten tonen dat, terwijl moeders in staat zijn positieve waarde toe te kennen aan hun ervaring met DBMD en tegelijkertijd ervaren dat er minder aandacht is voor hun behoeften wanneer de symptomen van het DBMD-kind ernstiger worden, hun veerkracht onder druk komt te staan naarmate zij ouder worden. Verder onderzoek is nodig om beter te kunnen begrijpen wat de effecten zijn van toenemende leeftijd en verergering van de functionele conditie van het kind op de psychosociale behoeften en noden, bevorderende factoren voor zorg, en psychologische adaptatie.

Klinische implicaties van de cross-sectionele en prospectieve studies over het welzijn van moeders zijn onder meer de behoefte aan systematische exploratie van factoren die de zorg bevorderen. Het gaat dan vooral om coping met DMD-gerelateerde onzekerheid en angst. Interventies om de adaptatie van moeders te verbeteren dienen gericht te zijn op versterking van hun veerkracht, en het kunnen zien en waarderen van de positieve aspecten van het hebben van een kind met DBDM. Clinici kunnen bij moeders onderzoeken, met gerichte vragen zoals die gebruikt werden in deze studie, wat hun specifieke noden en behoeften zijn.

Samenvattingen van de onderzoeksbevindingen zijn verspreid via de PPMD forums, zoals sociale media en het jaarlijks congres van de PPMD. De bevindingen van de studies

beschreven in dit proefschrift  werden gebruikt voor een wellbevinden-interventie op de jaarlijkse conferentie van de PPMD in 2013, en voor twee subsidieaanvragen over het welzijn van zorgverleners. Eind 2014 is op basis van dit proefschrift via DuchenneConnect, een programma gestart voor moeders van DBMD-kinderen. De longitudinale studie naar welbevinden van moeders is met een jaar uitgebreid waarbij ook gegevens worden verkregen over onzekerheid, spiritualiteit en hoop.

Hoofdstukken 3-5 beschrijven de studie naar **voorkeuren voor behandeling en impact,** In dit onderzoek werd gebruik gemaakt van de Best-Worst Scaling methode. Wij vonden dat verzorgers van een DBMD-kind bereid waren een verhoogde kans op een ernstige uitkomst tijdens een klinische trial te accepteren wanneer zij konden meedoen met een non-curatieve behandeling, zelfs zonder verbetering van levensverwachting. De studie leverde belangrijke informatie op voor beleid inzake het voornemen om specifieke klinische trials te starten. In de ‘zorgen’ studie zijn we erin geslaagd de meest belangrijke ‘zorgen’ te onderscheiden. Geconcludeerd kon worden dat de meest dringende zorgen betrekking hadden op symptoomprogressie, en toegang tot medische zorg, gevolgd door zorgen om het geluksgevoel van het kind. Van minder belang leken zorgen gerelateerd aan het welbevinden van ouders en de impact op het gehele gezin. Best-Worst Scaling is een krachtige methode om ziekte-percepties en ziekte-impact te exploreren en kwantificeren. De methode wordt nog weinig gebruikt in gezondheid-gerelateerde sociaalwetenschappelijke studies.

Van de in dit proefschrift beschreven studies had de behandelingspreferentie studie de meeste impact op zowel patiënten vertegenwoordiging als overheidsbeleid. We beschreven een procesmodel voor patiëntenorganisaties hoe geneesmiddelen op patiëntgerichte wijze kunnen worden ontwikkeld. De bevindingen werden voorgelegd aan vertegenwoordigers van de FDA (Food and Drug Administration) zodat deze konden worden gebruikt bij de beoordeling van toekomstige DMD therapieën. FDA-medewerkers vonden de het model eveneens toepasbaar voor andere patiëntenorganisaties[1] en benadrukten de behoefte aan nader onderzoek door andere organisaties.[2] Enkele biofarmaceutische bedrijven hebben het model uit deze studie gebruikt of willen dat gebruiken voor regelgeving. De studie werd ook geciteerd in de U.S. House of Representatives Energy and Commerce Committee 21st Century Cures Initiative en beschreven in een Committee Hearing.[3]

De PPMD had met de bevindingen van deze studie belangrijke argumenten in een overleg met

de FDA. Dit leidde er toe dat FDA de PPMD verzocht om een voorlopige handleiding te ontwikkelen voor DMD— de eerste voor een patiëntenorganisatie voor een zeldzame ziekte. Deze werd in juni 2014 aangeboden aan de FDA. De handleiding begint met een hoofdstuk over benefit/risk assessment, dat een samenvatting bevat van de bevindingen en dat sponsors adviseert om patiënt/verzorger preferenties mee te laten wegen in het proces van ontwikkeling van geneesmiddelen en regelgeving.[4]

Na afloop van de studie hebben de auteurs hun bevindingen gepresenteerd op meer dan 20 congressen en bijeenkomsten van patiëntenverenigingen. Twaalf patiëntenorganisaties van andere ziekten hebben belangstelling getoond voor gebruik van het model. Een voorbeeld van blijvende impact is de in november 2014 aangekondigde samenwerking tussen de PPMD en Santhera Pharmaceuticals om een nieuwe benefit/risk studie te doen naar pulmonaire therapie voor Duchenne.[5]

**Besluitvorming in klinische trials** (Hoofdstukken 6-8) is een gebied van toenemend belang voor sponsoren van klinische trials, onderzoekteams, ethische beoordelingscommissies, en patiëntenorganisaties. Onze studies toonden de complexiteit van besluitvorming in klinische trials, vooral binnen de context van een zeldzame, progressieve pediatrische ziekte. De deelnemende ouders stelden “niets doen” (d.w.z. niet deelnemen aan een trial) gelijk aan “schade toebrengen (doing harm)”. De beslissingen van ouders werden sterk beïnvloed door de kans op voordeel (benefit) voor het kind, maar de ouders toonden niet de therapeutische misconceptie. Optimisme volgend op de beschikbaarheid van een klinische trial was een ander voordeel dat hoog gewaardeerd werd door zowel de ouders als de in de trial betrokken clinici. Ouders zeiden dat zij, voorafgaand aan het proces van informed-consent, de voor- en nadelen al afwogen en het voornemen ontwikkelden om aan een klinische trial mee te doen.

Clinici dachten dat zij meer invloed hadden op het besluit van ouders dan door de ouders zelf aan clinici werd toegeschreven. Clinici voelden zich verantwoordelijk om geïnformeerde beslissingen mogelijk te maken en tegelijk het optimisme van ouders niet van hen af te nemen. Gebaseerd op onze bevindingen adviseren we clinici, sponsoren, en patiëntenorganisaties om een strategie c.q. handleiding te ontwikkelen voor deelname van families aan klinische trials waarbij kan worden geanticipeerd op potentieel ongewenste uitkomsten van de trial. Dit kan clinici ondersteunen in hun gesprekken met families en ook enige voorzorg bieden om beslissingsspijt te voorkomen.

We hebben ook beschreven hoe ouders de waargenomen benefits tijdens een klinische trial inschatten en waardeerden. Dit heeft implicaties voor de mate waarin zij in de trial blijven participeren. Deelnemers beschreven een complex proces van voortdurend wikken en wegen, en het inschatten van de voor- en nadelen. De meeste ouders zagen individuele voordelen voor hun kinderen, maar ook andere voordelen zoals altruïsme, nauwe band met het onderzoeksteam, en meer optimisme.

De bevindingen van de beide interviewstudies hebben bijgedragen aan de ontwikkeling van een kwantitatieve studie naar besluitvorming bij klinische trials. Voor toekomstig onderzoek worden onze kwalitatieve en kwantitatieve bevindingen gebruikt voor aanpassing van Leventhal's common-sense model voor zelf-regulatie. Dit model beschrijft de reacties op, en hanteren van bedreigingen van gezondheid[6]. Het aangepaste model houdt in dat bij beslissingen over het hanteren van een ziekte ook rekening moeten worden gehouden met verwachtingen en hoop als cognitieve en emotionele waarderingen die van invloed zijn op cognitieve en emotionele processen. Dit biedt een kader waarmee besluitvormingsprocessen in de context van klinische trials kunnen worden vastgesteld. Een volgende stap is de ontwikkeling en evaluatie van een beslissingshulp waarmee verwachtingen en optimistische hoop in klinische trials van elkaar kunnen worden onderscheiden.

Gegevens van deze studies zijn gepresenteerd aan sponsoren van klinische trials. Verder aan het Patient Centered Outcomes Research Institute, de Clinical and Translational Science Award (CTSA) program, aan clinici-onderzoekers op de World Muscle Society en andere professionele forums, en aan patiënten en families via de PPMD forums. De resultaten zijn gebruikt voor de ontwikkeling van nieuw voorlichtingsmateriaal voor patiënten en families, en gepresenteerd in sessies over verwachtingen over klinische trials tijdens de jaarlijkse PPMD conferentie. Tot slot, diverse thema's van deze studie zijn opgenomen in studies naar besluitvormingsprocessen in andere patiëntengroepen (spinal muscular atrophy, Fragile X syndrome, and HIV).

**Implicaties voor CEnR benaderingen**

Tabel 2 toont de benaderingen voor CEnR die in dit proefschrift zijn gebruikt. We vonden dat betrokkenheid van diverse stakeholders in wetenschappelijke studies op niveau 1 of hoger op het continuüm belangrijk is voor het stellen en beantwoorden van onderzoeksvragen. De bruikbaarheid en geschiktheid van hogere niveaus van de betrokkenheid van de stakeholders

varieert op basis van tijdslijn van het programma, het beschikbare budget, en de behoeften. De CBPR (Community based participatory research) benadering in de studie naar klinische trials gaf veel informatie maar vereiste veel tijd en een budget dat niet altijd beschikbaar was. In de behandelingspreferentie-studie hebben de onderzoekers en de adviesraad er voor gekozen om met een breed spectrum aan stakeholders te spreken over de behoefte aan, en de implicaties van de studie. Stakeholders waren ook van belang voor het bepalen van de attributies en niveaus van het model. Een 'hybride' betrokkenheid van de stakeholders bij wetenschappelijke studies bleek vanzelfsprekend in onderzoek binnen patiëntenorganisaties; studies kunnen dan rekenen op medewerking en respect.

**Tabel 2. Rating of Community-Engaged Research Approaches**

| **Study** | Studie naar welbevinden van moeders | Duchenne Behandelings-preferenties | Klinische Trial Verwachtingen Pilot | Klinische Trial Verwachtingen en Ervaringen |
|---|---|---|---|---|
| **A. Inclusie van stakeholders in ontwikkeling van research program** | Niveau 3 | Niveau 2 (+ significante bijdrage aan ontwikkeling van items) | Niveau 1 | Niveau 3 |
| **B. Inclusie van stakeholders in besluitvorming** | Niveau 2 | Niveau 2 | Niveau 1 | Niveau 3 |
| **C. Vergroten van stakeholders' adviserend vermogen tav onderzoek** | Niveau 2 | Niveau 2 | Niveau 1 | Niveau 3 |
| **D. Verspreiden van studie informatie** | Niveau 3 | Niveau 3 | Niveau 1 (+ leken samenvatting) | Niveau 3 |
| **E. Ontwikkeling van aanbevelingen over beleid, diensten en interventies** | Niveau 2 | Niveau 3 | Niveau 2 | Niveau 3 |

**Lessen over betrokkenheid van patiënten, families, en andere stakeholders in wetenschappelijk onderzoek**

We hebben de volgende lessen geleerd over betrokkenheid van de stakeholders bij onderzoek.

- In de studie naar welbevinden van moeders werd getoond hoe belangrijk het is om de ziekte-ervaringen in context te zien. De bevindingen onderstrepen de behoefte om anders dan in voorgaand onderzoek te kijken naar positieve voorspellende en uitkomstvariabelen van welbevinden.
- In de behandelingspreferentie studie, werd het belang en noodzaak gezien van flexibiliteit bij de onderzoeker wanneer sprake is van bepaalde reacties bij de stakeholders. Zelfs al zij stakeholders betrokken bij de opzet van het onderzoek, dan nog zal niet iedereen in de stakeholders het eens zijn over de waarde van het verstrekken van kwantitatieve gegevens aan de regelgevers. We voegden derhalve een complementaire benadering toe (PPMD's "Vertel uw Verhaal" [7]) om de aanvaardbaarheid bij de stakeholders te vergroten en onze waardering te tonen voor de kracht van gezins- en familie participatie.
- De klinische trial studies toonden de voordelen van een zeer betrokken CBPR benadering voor het onderzoeken van complexe ethische problemen met implicaties voor een brede range van stakeholders. Het incorporeren van een brede range van ervaren stakeholders in het proces was van belang voor het kaderen van ethische vragen.

De betrokkenheid van stakeholders in de in dit proefschrift beschreven studies had belangrijke, soms verstrekkende impact op de doelen van de studies, het design, analyses, interpretatie en verspreiding van bevindingen. Er is waarschijnlijk geen one-size-fits-all benadering voor het betrekken van stakeholders bij wetenschappelijk onderzoek. Sterker, betrokkenheid van stakeholders vraagt om een aanpak die stakeholders in staat stelt om goed te begrijpen wat de onderzoeksagenda inhoudt en dat zij daarop invloed kunnen uitoefenen. Lange-termijn betrokkenheid vraagt om educatie en ondersteuning zodat ouders en verzorgers zich iets kunnen voorstellen bij onderzoek en vervolgens actief kunnen participeren in het vaststellen van de onderzoeksagenda. Onderzoekers moeten open staan voor verandering en appreciëren dat hun eigen perspectief en onderzoekservaring zich alleen maar kunnen verbreden en verdiepen als zij patiënten, families en andere stakeholders bij hun onderzoek betrekken.

REFERENCES

1. Food and Drug Administration “Complex Issues in Rare Disease Drug Development” public workshop, Jan 7 2014, Maryland USA
2. The Pink Sheet. “Woodcock Encourages Patient Groups To Take Lead To Speed Regulatory Process, Development.” July 11 2014 Available at https://www.pharmamedtechbi.com/publications/the-pink-sheet-daily?issue=Jul-11-2014
3. Testimony of Pat Furlong Parent Project Muscular Dystrophy, Committee on Energy & Commerce Subcommittee on Health July 11, 2014 available at http://democrats.energycommerce.house.gov/sites/default/files/documents/Testimony-Furlong-HE-21st-Century-Cures-Incorporating-Patient-Perspective-2014-7-11.pdf
4. Parent Project Muscular Dystrophy, “FDA Draft Guidance on Duchenne” 2014. Available at http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance
5. Parent Project Muscular Dystrophy, “PPMD and Santhera Pharmaceuticals Team Up on New Benefit/Risk Study Focused on Pulmonary Therapies” 2014. Available at http://community.parentprojectmd.org/profiles/blogs/ppmd-and-santhera-pharmaceuticals-team-up-on-new-benefit-risk
6. Leventhal, H., Nerenz, D. R., & Steele, D. J. (1984). Illness representations and coping with health threats. In A. Baum, S. E. Taylor, & D. J. Singer (Eds.), Handbook of psychology and health: Social psychological aspects of health (Vol. 4, pp. 219–252). Hillsdale, NJ: Erlbaum.
7. Parent Project Muscular Dystrophy. “Patients are Waiting” 2014. Available at http://www.parentprojectmd.org/site/DocServer/SYS.pdf?docID=15643

# Appendices

# Appendix 1. List of Co-Authors and Affiliations

Barbara Biesecker, PhD: Social and Behavioral Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda MD, USA

Janice Bowie, PhD: Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

Ethan Brenna, BS: Social and Behavioral Research Branch, National Human Genome Research Institute, Bethesda MD, USA

John Bridges, PhD: Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

Diana Escolar, MD: Department of Neurology, Kennedy Krieger Institute, Baltimore MD, USA

Ryan Fischer, BA: Vice President of Community Engagement, Parent Project Muscular Dystrophy, USA

Tyler Fisher, BS: Social and Behavioral Research Branch, National Human Genome Research Institute, Bethesda MD, USA

Pat Furlong, MS: President, Parent Project Muscular Dystrophy, USA

Ilene Hollin, MPH: Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA

Joanna Johnson, MEd: Parent Advocate, Parent Project Muscular Dystrophy, USA

Kathleen Kinnett, MSN: Vice President Clinical Care, Parent Project Muscular Dystrophy, USA

Bettina Meiser, PhD: Prince of Wales Clinical School, University of New South Wales, Sydney, Australia

Kanneboyina Nagaraju, PhD, DVM: Center for Genetic Medicine Research, Children's National Medical Center, Washington DC, USA

Jonathan Piacentino: Patient Self Advocate, Parent Project Muscular Dystrophy, USA

Kathryn Porter, JD: Research Coordinator, Parent Project Muscular Dystrophy, USA

Hadar Scharff, MPH: Research Coordinator, Parent Project Muscular Dystrophy, USA

Aad Tibben, PhD: Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands

Benjamin Wilfond, MD: Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute, Seattle WA, USA

# Appendix 2. Curriculum Vitae

Holly Landrum Peay was born on 15 February in Washington, DC, USA. She grew up in Virginia and attended college at the University of Virginia. In 1995 she graduated with distinction with a Bachelor of Arts in Interdisciplinary Studies in Biomedical Ethics. Holly then attended the University of South Carolina School of Medicine, where she received a Masters of Genetic Counseling degree in 1997.

Holly has a range of professional experience, including developing healthcare provider education programs for the National Coalition for Health Professional Education in Genetics; providing clinical genetic counseling for neuropsychiatric disorders at the Greater Baltimore Medical Center and the National Institutes of Health; and acting as Associate Director of the Master's Program in Genetic Counseling at the National Human Genome Research Institute and Staff Scientist at the Social and Behavioral Research Branch. She has received numerous grants for educational and research projects. Holly was elected to the American Board of Genetic Counseling and the Accreditation Council for Genetic Counseling. She holds an adjunct faculty appointment at the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, USA.

In 2010 she started studies for her PhD (Prof. Aad Tibben). At present she is Senior Vice President for Community Research at Parent Project Muscular Dystrophy and Director of the DuchenneConnect registry, where she is Principal Investigator of a PCORnet award from the Patient Centered Outcomes Research Institute. In addition, she is a Guest Researcher at the Social and Behavioral Research Branch, National Institutes of Health and a consultant with the United States Military HIV Research Program.

# Appendix 3. List of Publications

Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K, Kosma K, Dawkins H, Lamont L, Roy AJ, Chamova T, Guergueltcheva V, Chan S, Korngut L, Campbell C, Dai Y, Wang J, Barišić N, Brabec P, Lahdetie J, Walter MC, Schreiber-Katz O, Karcagi V, Garami M, Viswanathan V, Bayat F, Buccella F, Kimura E, Koeks Z, van den Bergen JC, Rodrigues M, Roxburgh R, Lusakowska A, Kostera-Pruszczyk A, Zimowski J, Santos R, Neagu E, Artemieva S, Rasic VM, Vojinovic D, Posada M, Bloetzer C, Jeannet PY, Joncourt F, Díaz-Manera J, Gallardo E, Karaduman AA, Topaloğlu H, Sherif RE, Stringer A, Shatillo AV, Martin AS, Peay HL, Bellgard MI, Kirschner J, Flanigan KM, Straub V, Bushby K, Verschuuren J, Aartsma-Rus A, Beroud C, Lochmüller H. The TREAT-NMD DMD Global database: Analysis of More Than 7000 Duchenne Muscular Dystrophy Mutations. Hum Mutat. 2015 Jan 21 [Epub ahead of print].

Lorio JG, Peay HL, and Mathews KD. Recognition and management of motor delay and muscle weakness in children. Am Fam Physician. 2015;91(1):38-44.

Peay HL and Henderson GE. What motivates participation in HIV cure trials?
A call for real-time assessment to improve informed consent. *Journal of Virus Eradication*, 2014 [Epub ahead of print].

Ilene L. Hollin, Holly L. Peay, John F.P. Bridges. Caregiver preferences for emerging Duchenne Muscular Dystrophy treatments: A comparison of best-worst-scaling and conjoint analysis. *The Patient*, December 2014 [Epub ahead of print].

Richard T. Wang, Cheri A. Silverstein Fadlon, J. Wes Ulm, Ivana Jankovic, Ascia Eskin, Ake Lu, Vanessa Rangel Miller, Rita M. Cantor, Ning Li, Robert Elashoff, Anne S. Martin, Holly L. Peay, Nancy Halnon, Stanley F. Nelson. Online self-report data for Duchenne muscular dystrophy confirms natural history and can be used to assess for therapeutic benefits. *PLoS Currents Muscular Dystrophy* Oct 17, 2014 [Epub ahead of print].

Nagy R, Peay H, Hicks M, Kloos J, Westman R, Conway L, Finucane B, Fitzpatrick J, Gordon E, Ramos E, Sekhon-Warren J, Silver J, Walton C, Reiser C. Genetic counselors' and genetic counseling students' attitudes around the clinical doctorate and other advanced educational options for genetic counselors: A report from the Genetic Counseling Advanced Degree Task Force. *J Genet Couns.* 2014 Oct 30.

Peay HL, Hollin I, Fischer R, Bridges JFB. A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. *Clinical Therapeutics* 2014;36:624–637.

PCORnet PPRN Consortium, Daugherty SE, Wahba S, Fleurence R. Patient-powered research networks: building capacity for conducting patient-centered clinical outcomes research. *J Am Med Inform Assoc.* 2014 May 12. doi: 10.1136/amiajnl-2014-002758.

Hooker GW, Peay H, Erby L, Bayless T, Biesecker BB, Roter DL. Genetic literacy and patient perceptions of IBD testing utility and disease control: a randomized vignette study of genetic testing. *Inflamm Bowel Dis.* 2014 May;20(5):901-8.

Peay HL, Tibben A, Fisher T, Brenna E, and Biesecker BB. Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy. *Clinical Trials.* 2014 Feb;11(1):77-85.

Peay HL, Rosenstein DL, and Biesecker BB. Parenting with bipolar disorder: Coping with risk of mood disorders to children. *Social Science and Medicine.* 2014 Mar;104:194-200.

Peay HL, Rosenstein DL, and Biesecker BB. Adaptation to bipolar disorder and perceived risk to children: A survey of parents with bipolar disorder. *BMC Psychiatry.* 2013 Dec 2;13:327.

Bladen CL, Rafferty K, Straub V, Monges S, Moresco A, Dawkins H, Roy A, Chamova T, Guergueltcheva V, Korngut L, Campbell C, Dai Y, Barišić N, Kos T, Brabec P, Rahbek J, Lahdetie J, Tuffery-Giraud S, Claustres M, Leturcq F, Ben Yaou R, Walter MC, Schreiber O, Karcagi V, Herczegfalvi A, Viswanathan V, Bayat F, de la Caridad Guerrero Sarmiento I, Ambrosini A, Ceradini F, Kimura E, van den Bergen JC, Rodrigues M, Roxburgh R, Lusakowska A, Oliveira J, Santos R, Neagu E, Butoianu N, Artemieva S, Rasic VM, Posada M, Palau F, Lindvall B, Bloetzer C, Karaduman AA, Topaloğlu H, Inal HS, Oflazer P, Stringer A, Shatillo AV, Martin AS, Peay H, Flanigan KM, Salgado D, von Rekowski B, Lynn S, Heslop E, Gainotti S, Taruscio D, Kirschner J, Verschuuren J, Bushby K, Béroud C, Lochmüller H. The TREAT-NMD Duchenne muscular dystrophy registries: conception, design and utilisation by industry and academia. *Human Mutation.* Aug 2 (2013) doi: 10.1002/humu.22390.

Schrans DG, Abbott D, Peay HL, Pangalila RF, Vroom E, Goemans N, Vles JS, Aldenkamp AP, Hendriksen JG. Transition in Duchenne muscular dystrophy: An expert meeting report and description of transition needs in an emergent patient population. *Neuromuscular Disorders.* Mar;23(3):283-6 (2013).

Yudell M, Tabor HK, Dawson G, Rossi J, Newschaffer C; Working Group in Autism Risk Communication and Ethics. Priorities for autism spectrum disorder risk communication and ethics. *Autism.* Nov;17(6):701-22 (2013).

Biesecker BB, Peay HL. Genomic sequencing for psychiatric disorders: promise and challenge. *International Journal of Neuropsychopharmacology*. Aug;16(7):1667-72 (2013).

Rangel Miller V, Martin AS, and Peay HL. DuchenneConnect registry report. *PLoS Currents: Muscular Dystrophy.* Version 2. Feb 29 (2012).

Peay HL, Hooker G, Kassem L, Biesecker BB. Family risk and related education and counseling needs: Perceptions of adults with bipolar disorder and siblings of adults with bipolar disorder. *American Journal of Medical Genetics*. Feb 1:149A(3):364-371 (2009).

Peay HL, McCarthy-Veach P, Gettig B, Palmer C, Rosen-Sheidley B, and Austin JC. Psychiatric disorders in clinical genetics I: Addressing family histories of psychiatric illness. *Journal of Genetic Counseling.* 17(1): 6-17 (2007).

Austin JC, Palmer C, Rosen-Sheidley B, McCarthy-Veach P, Gettig B, and Peay HL. Psychiatric disorders in clinical genetics II: Individualizing recurrence risks. *Journal of Genetic Counseling.* 17(1): 18-29 (2007).

Austin JC and Peay HL. Applications and limitations of empiric data in provision of recurrence risks for schizophrenia: a practical review for healthcare professionals providing clinical psychiatric genetics consultations. *Clinical Genetics.* Sep;70(3):177-87 (2006).

Biesecker, BB and Peay H L. Ethical considerations in psychiatric genetics research: points to consider. *Psychopharmacology (Berl*). 171(1), 27-35 (2003).

Rackover MA, Peay HL, and Wolpert CM. The need for genetic literacy in physician assistants. *Perspective on Physician Assistant Education*. 12, 113-116 (2001).

## Books and Book Chapters

Peay H and Austin J. How to Talk with Families about Genetics and Psychiatric Illness. W.W. Norton and Company, New York, 2011.

Peay HL and Hadley D. *Genetic Counseling,* in Kaplan & Sadock's Comprehensive Textbook of Psychiatry 9th Edition, ed. Sadock BJ, Sadock VA, Ruiz P: Lippincott Williams & Wilkens, 2009 (invited chapter update submitted, 2015)

Peay HL and Rosen-Sheidley B. *Principles of Genetic Counseling: Application to Psychiatry*, in Psychiatric Genetics: Applications in Clinical Practice, ed. Smoller JW, Tsuang MT, Rosen-Sheidley B: American Psychiatric Publishing, 2008.

# Appendix 4. Acknowledgements

I gratefully acknowledge Profs. Aad Tibben and Bettina Meiser, who are gifted thesis supervisors and allowed me great latitude to follow research paths identified during community engagement. It was a fantastic experience and I am honored to have learned from you both.

To my review committee, I thank you for your thoughtful read and discussion.

To my community engagement partners and my colleagues at Parent Project Muscular Dystrophy, you truly led the way.

And finally I acknowledge my family for their tolerance during this time of intense professional focus. Too many times I heard my children ask, “Could you please just sit in the same room with me? You can bring your laptop….” Thank you for your love and patience, and for continuing to invite me into your rooms now that I can occasionally part with my laptop.