PATIENT-CENTERED DRUG DEVELOPMENT IN RARE DISEASES: THE CASE OF DUCHENNE MUSCULAR DYSTROPHY

by
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Abstract

Problem Statement

Patient-centeredness has gained favor in recent years. Drug development researchers increasingly acknowledge that patient preferences can contribute valuable information to decision-making. The importance of incorporating patient preferences is underscored for rare disease populations in which clinicians and researchers have limited experience with the condition and the disease experience is best understood by patients. This dissertation aims to measure preferences among caregivers and patients with Duchenne muscular dystrophy (DMD).

Methods

This body of work is based on a two online surveys intended for caregivers and patients with DMD. Survey respondents were recruited via a patient registry and snowball sampling. The surveys were designed using a community-engaged approach and included best-worst scaling (BWS) case 1, case 2 and conjoint-analysis. The main analytic methods included latent class analysis, mixed logistic regression and conditional logistic regression.

Results

Chapter 3 demonstrates a successful process for community engagement in survey development that affected eligibility criteria, attribute refinement, and revealed the delicate nature of mapping clinical trial endpoints to meaningful survey objects. Chapter 4 findings indicate that caregivers and patients do not differ in their priorities for signs and symptoms to be targeted by therapeutic interventions. However, priority heterogeneity does exist and may be related to unobserved characteristics. Chapter 5 findings reveal patients are willing to accept significant risk in order to

have the benefit of moderate improvements in pulmonary decline. Finally, methodological findings in Chapter 6 indicate that conjoint analysis combined with BWS provides policy-relevant information about the intention to use therapy and serves to validate the BWS method.

Conclusions

This research contributes to the overall body of knowledge around patient preferences in DMD and as a result may improve the usefulness of future drug development. It also measures patient preferences for a pulmonary benefit, information that will be incorporated into regulatory review. There are implications for the broader rare disease community: this dissertation demonstrates a model for how to undergo this research and underscores the importance of preference work to meet the unique needs of the rare disease community.

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If I have seen further, it is by standing on the shoulder of giants.

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Chapter 1

Introduction

1.1 Patient-centered benefit-risk assessment

Patient-centered benefit-risk (PCBR) assessment is the increasingly favored view of incorporating patient preference information into regulatory decision-making. Patient preference information is generally concerned with how patients and families make decisions about their health and healthcare, but in a PCBR context, patient preference information refers specifically to how patients make decisions about new technologies such as drugs or medical devices. The aim of PCBR is to understand how patients value benefits and risks and how they consider benefit-risk tradeoffs, including quantifying risk tolerance, maximum acceptable risk, and minimum required benefit.

When a New Drug Application is submitted to the FDA, a team of scientists, including physicians, statisticians, toxicologists, pharmacologists, and chemists review the data and proposed labeling to establish if the drug's benefits outweigh its known risks. FDA considers whether or not the drug is safe and effective in its proposed use and whether the benefits outweigh the risk [1]. Only those sitting around the table at the time of the decision are privy to the intricacies of the process. The benefit-risk framework used to make the decision includes five decisions factors: 1) analysis of condition, 2) current treatment options, 3) benefit, 4) risk and 5) risk management [2]. The first two factors are not drug-specific considerations, but are considerations for the therapeutic area. The last three factors are drug-specific considerations. All the factors are dynamic and can be updated as

new information becomes available. For the therapeutic area considerations, this information represents the current state of knowledge regarding the condition and available therapies and changes as new drugs enter or exit the market and as new information about the disease becomes available. For the drug-specific considerations, this can be updated as new information about benefits and risks becomes available throughout the drug lifecycle (i.e. post-approval).

Patient preferences are noticeably absent from this regulatory benefit-risk framework. Historically, patient involvement in the regulatory process has been minimal. A patient representative, or in some cases a few representatives, have been included on the expert advisory panels. However, this is limited to qualitative data that is not necessarily representative of the breadth of patient perspectives. It is unknown how this information, if at all, is incorporated in the regulatory decision-making process. Details about traditional regulatory benefit-risk assessment are elusive [3-4]. PCBR is a logical extension of benefit-risk assessment in which the patient's perspective is considered in evaluation of the safety and efficacy of a new technology.

1.2 History of patient-centered drug development

In the United States, the Food and Drug Administration (FDA) is a powerful regulatory agency that authorizes drugs and medical devices to be legally marketed after the agency deems them safe and efficacious [5]. In this way, the FDA serves as a very powerful gatekeeper to the pharmaceutical marketplace. The Prescription Drug User Fee Act (1992) provided a supplemental revenue source for the agency by authorizing the FDA to charge pharmaceutical companies fees. Patient perspectives were first incorporated into drug development when PDUFA was reauthorized by Congress in 1997 as part of the Food and Drug Administration Modernization Act; it aimed to facilitate better communications between pharmaceutical companies and patient advocacy groups. Patients weren't systematically and earnestly included until the fifth reauthorization in 2012, which was included in Food and Drug Administration Safety and Innovations Act (FDASIA). The Prescription Drug User Fee Amendments of 2012 (PDUFA V) called for upgrading benefit/risks assessments and more patient perspectives in the drug review process. The Secretary was charged with developing and implementing strategies to

solicit patient perspectives during the development process and to consider those preferences during regulatory discussions by "fostering participation" of patient representatives [6].The expansion of PCBR assessment also includes consideration of current treatment options as well as the severity of the condition, but does not include patient preferences.

Since PDUFA V, and since the ACA has more generally directed the country towards patient-centered healthcare, US regulatory agencies have made a concerted effort to understand the perspective of the patient. The Center for Drug Evaluation and Research (CDER), the office within the FDA responsible for regulating drugs, launched the Patient Focused Drug Development (PFDD) initiative. This initiative offers a systematic way to collect information about the patient's perspectives on disease severity, available treatments, and how drugs can better meet their needs. It has conducted or plans to conduct 20 meetings over the course of 5 years, each focused on a specific disease area. Following each meeting, a "Voice of the Patient Report" summarizes the content. A concerted effort was made to target disease areas that are 1) chronic, symptomatic and affect functioning, 2) for which aspects of the disease are not fully captures in clinical trials, 3) diseases with limited or no current therapies, and 4) diseases with severe impact on identifiable subpopulations such as children or the elderly. Recognizing what a small percentage of diseases would be covered by only 20 meetings, the FDA also invited outside organizations to organize externally led PFDD meetings using the FDA model [7]. Similar efforts are occurring throughout the European Medicine Agency (EMA), the European counterpart to the FDA [8].

Concurrently, the Center for Devices and Radiological Health (CDRH), the office of the FDA responsible for regulating medical devices and radiation-emitting products, launched the Patient Preference Initiative to identify and develop methods for assessing patient preferences of benefit and risk related to specific device types and specific illnesses and conditions. Although both CDER and CDRH are both playing a role in shaping patient-focused drug development, many of the advances specific to PCBR have occurred within CDRH and the Center for Biologics Evaluation and Research (CBER), the branches of the FDA responsible for the approval of all medical devices, biologics and related products. CDRH and CBER

published a draft guidance on benefit-risk in 2012 stating that FDA reviewers may consider patients perspectives when such information is available [9]. A later document in 2015 expanded on this to advise what patient preference information may be used by FDA and highlighted its importance for preference-sensitive decisions in which there is significant uncertainty and patients' views differ considerably from those of researchers and clinicians [10]. This guidance document also acknowledges the variation in patient preferences and enumerates how and when the FDA might consider patient preference information during its review process. The FDA acknowledges that quantitative patient preference assessment is an evolving research area. Furthermore, in early 2015, the CDRH published its first preference study intended to inform regulatory decision-making. This included presenting relative value for attributes of weight-loss devices and a tool to estimate minimal acceptable benefit and maximum acceptable risk [11].

To date, the FDA has not provided detailed instructions on how device developers should collect and use this information. To that end, the Medical Device Innovation Consortium (MDIC), a public-private partnership made up of key stakeholders, has developed a framework for incorporating patient preference information regarding benefit and risk into regulatory assessment of new technologies [3]. The framework report released in May 2015 provides background on PCBR, discusses the value of PCBR in the regulatory context, provides guidance on circumstances in which PCBR is valuable, appropriating timing for PCBR's use in the development lifecycle, and offers advice on how to collect and use preference information including a catalog of appropriate methods.

1.3 PCBR for rare diseases

As the recipients of treatment, all patients have a distinctive role in benefit-risk assessment and regulatory decision-making. However, patients with rare diseases have a particularly important role to play. Current PCBR information sources highlight rare diseases as an appropriate context for patient preference information because treatment choices are laden with preference-sensitive decisions due to high levels of uncertainty. Furthermore, reviewers' limited clinical experience with rare diseases means that patient preferences likely differ significantly from those

of reviewers and clinicians and therefore patient preference information may be highly relevant [3]. Additionally, in the rare disease context patient preferences are imperative to either confirm or contradict assumptions about extremely high risk-tolerance thresholds in the face of high mortality, severe morbidity and a scarcity of treatment options.

1.4 Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a rare, life-shortening, inherited neuromuscular disorder that occurs in 1.3-2.9 per 10,000 males [11-12]. Onset occurs early in life with symptoms first appearing in early infancy and diagnosis typically occurring around age 5, when motor function typically develops [14-15]. DMD is characterized primarily by progressive muscular weakness and loss of ambulation in their teen years [14,16]. It also involves expected pulmonary decline [17-21]. It ultimately results in premature death in the boy's second and third decade most frequently as a result of respiratory failure from pneumonia with cardiac involvement [14-15]. There are currently no FDA-approved therapies for DMD, and the gold standard for treatment relies on off-label use of corticosteroids, which has shown to have some benefits with regards to slowing the loss of muscle loss, delaying loss in ambulation by 2-5 years, improving cardiopulmonary function and enhancing quality of life [14, 22-24].

This disease makes for an interesting context in which to study patient centered benefit-risk assessment because patient and caregivers are actively involved in advocating for accelerated drug approvals, encouraging regulatory permissiveness and demanding access [25-27]. There are also many preference sensitive decisions due to significant care-related burden, financial burden, the vulnerability of a pediatric population and caregivers often being the primary decision-maker, and of course the natural history of the disease [27-30]. Finally, DMD is an ideal population for this research because the community's advocacy leadership have been active participants and leaders in advocating for patient-centered benefit-risk assessment [31].

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Chapter 2

Methods

Stated-preference methods are a research method to objectively and scientifically measure consumer preferences based on hypothetical scenarios. These methods contrast revealed preferences in which consumer behavior is observed in real markets. A key disadvantage of revealed preferences is that its use is limited to existing goods and services. Stated-preference methods on the other hand, are designed to understand how consumers may behave toward a hypothetical good and are therefore ideal for incorporating patient preferences into patient-centered drug development - a context in which regulators have to weigh benefits, risks, and their relative importance for a hypothetical good under a great deal of uncertainty.

2.1 Best-worst scaling

In evaluating trade-offs, choice-based preference measurement such as conjoint analysis are useful. Conjoint analysis is designed to measure choice behavior. Discrete choice experiments (DCE) has been the traditional technique for preference elicitation and widely used in healthcare [1-2]. Best-worst scaling was introduced by Finn and Louviere in 1992 and its formal statistical and theoretical properties were proven by Marley and Louviere in 2005 [3-4]. Although McIntosh and Louviere first introduced BWS to healthcare research in 2002, and it has become increasingly used in healthcare, it is still lesser-known compared to other choice-based approaches [5-8]. A full catalog of stated-preference methods for assessing patient preferences for patient-centered benefit-risk are available [9].

Best-worst scaling (BWS) is a form of conjoint analysis that presents survey

respondents with an attribute set (or attributes and levels set) of three or more items from which the respondent identifies the best and worst items [10]. The attribute set can be thought of as characteristics of a good. BWS in particular, and choice-based modeling in general, is an application of consumer theory in which utility is derived from a particular bundle of characteristics rather than from a good itself [11]. The underlying assumptions of BWS are that that the choices themselves represent the extremes of a latent, subjective continuum [10].

There are three types of BWS: object case, profile case, and multi-profile case [3,6]. In the object case (case 1) respondents evaluate a list of independent objects, similar to how one evaluates a ranking scale [6]. The design is intended to assess relative preferences for a series of objects. Examples of its use in healthcare include investigating opinions about food supply policy and to guide health reform in Australia [3,13]. In the profile case (case 2) respondents evaluate a single profile at a time, made up a series of attributes with different levels assigned, and choose the best and worst attribute/level combinations from within that profile [6,14]. In the multi-profile case (case 3), respondents evaluate sets of multiple profiles together at a time and choose the best and worst overall profile [6,15]. BWS case 1 and 2 are the dominant variants in healthcare with applications that include eliciting utility weights, evaluating treatments and interventions, measuring workforce preferences, and identifying criteria for policy decisions such as budget allocation and priority-setting [8]. The enclosed studies concern BWS case 1 and 2. For either type, the response pattern can be analyzed to estimate the relative importance among the attributes (case 1) or attributes and levels (case 2).

2.2 Theory

BWS as probabilistic discrete choice models have been well-established [4,16]. These models, based in random-utility theory, are consistent with neoclassical economic theory [11,17-19]. Random-utility theory suggests that the decision process is considered to be deterministic and the utilities are stochastic. Economists interpret the probabilistic nature of the models such that researchers are unable to measure all factors that impact the choice. An alternative theory for discrete choice modeling suggests the decision process is random and the utilities are determinis-

tic. The psychology discipline subscribes to this fixed utility theory and interprets the probabilistic natures of the models as a result of inconsistencies in human decision-making [20]. Summaries outlining how the two disciplines approach the decomposition of the probabilistic process and its application to BWS have been published elsewhere [10]. Regardless of discipline, as researchers, we must simplify the complexity of human decision-making process with models.

Max-difference (paired) models assume that individuals consider all of the possible pairs of best and worst and choose the pair that maximizes the difference between them. Parameters and log-likelihood can be correctly estimated using a standard conditional (multinomial) logistic regression command (implemented via the paired MNL method). Marginal models consider the best and worst choices separately; as such, they may be considered to be more realistic than paired ones. Choices can be made simultaneously or sequential. In this dissertation sequential best-worst scaling is used, which introduces a trivial error to the log-likelihood but is more consistent with how the data are collected [6]. This analysis relies on an essential assumption that the choice of the best and worst item represents the farthest different between the degree of importance among any item on an underlying ranking of item importance [21]. Econometrics operationalization of BWS data in a random utility model parallels that of a traditional DCE [6,22]. In acknowledgement that the extreme choices on either end of latent, subjective continuum are not necessarily equivalent to a choice being considered acceptable or unacceptable [10], a second-order opt out question to measure actual intention to use treatments is incorporated into the experiment as well.

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 [23]. BWS places greater emphasis on item importance, whereas conjoint analysis emphasizes trade-offs and more closely represents a real decision [24]. Furthermore, best-worst scaling has the added advantage of its ability to estimate conditional attribute importance, which is the estimated utility associated with a particular attribute, with no reference to associated levels.

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Chapter 3

Developing a Patient-Centered Benefit-Risk Survey: A Community-Engaged Approach

[1] [2]

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3.1 Abstract

Background We provide a community-engaged process to inform the design of a stated preferences experiment. The process involves integrating patients and caregivers of people with Duchenne/Becker muscular dystrophy, advocates, clinicians, and the sponsor in conceptualizing and developing a benefit-risk survey based on phase III trial results.

Methods Our community engagement process for development of a stated-preference survey includes a set of five guiding principles with foundations in the principles of community-engaged research. Engagement efforts were carried out through an informal network of 3 committees. Members of leadership, stakeholder and review committees comprised of patients, caregivers, clinicians, advocacy leadership, and industry representatives.

Results Committee members participated in 15 hours of formal engagement including interviews and conference calls that ranged from 45 - 90 minutes, plus additional less-formal ad hoc communication. Committees were comprised of 20 individuals across 3 committees including adults with Duchenne muscular dystrophy (n=6), parents of children with Duchenne muscular dystrophy (n=6), clinicians (n=3), members of research and advocacy organizations (n=4), and an industry representative (n=1). Community engagement informed attribute selection, survey length, word choice, and eligibility criteria. Challenges in the process included managing diverse stakeholder perspectives, time requirements, and the inherent tension between outcomes used in clinical trials versus attributes that correspond to patient and family-relevant outcomes.

Conclusions We demonstrate how community engagement can successfully influence study design to support the design of a relevant survey instrument that is ethical, acceptable, meaningful to the community, and enhances patient-centered benefit-risk assessment for regulatory decision-making.

3.2 Background

Patient-centered benefit-risk assessment (PCBR) is the science of assessing patient preferences regarding benefit- risk tradeoffs. Applied to a regulatory context, PCBR refers to using information about how patients consider benefit-risk tradeoffs in regulatory decision-making. Historically, the U.S. Food and Drug Administration (FDA) has considering primarily the regulatory and researcher perspectives in benefit-risk assessment for approvals. Recently, however, there has been increasing recognition of the value of the patient and caregiver perspectives in regulatory decision-making. In 2012, as part of the FDA Safety and Innovation Act (FDASIA) the agency committed to further development of its Benefits Risk Assessment Framework, integration of the framework into the review process, and established a five-year Patient Focused Drug Development program intended to increase stakeholder involvement in regulatory processes [1-2]. Evidence of a shifting paradigm in favor of patient-centeredness is further reflected in FDA guidance documents that represent current thinking and serve as a set of recommendations for industry and regulators. A 2012 guidance from the Centers for Devices and Radiological Health (CDRH) listed patient preferences among factors to consider when making benefit-risks determinations in medical device approvals [3]. In 2013, the FDA invited Parent Project Muscular Dystrophy (PPMD), an advocacy organization focused on finding a cure for Duchenne and Becker Muscular Dystrophy (DBMD), to write the first patient-advocacy-initiated draft guidance [4]. In June 2014, PPMD submitted a draft guidance to the FDA to help accelerate drug development and review of DMD therapies [5]. One year later, the FDA released its own guidance on DMD and related disorders, which included a statement that regulatory decisions would consider patient and caregiver risk tolerance in light of the life threatening nature of the condition [6].

PCBR studies require methods that produce representative, scientific data to quantify preferences and directly inform regulatory review [7]. PCBR stakeholders have cataloged methods, published checklists and developed frameworks for using these methods [8-9], but less attention has been paid to when and how to include patients and other stakeholders. The PPMD draft guidance recommends industry sponsors engage with patients and families early in drug development and

partner with advocacy organizations to better understand meaningful benefits and risk tolerance [5]. Furthermore, the guidance recommends that sponsors engage in community-centered research, including patient-centered efforts, to obtain preference information if it does not already exist, and use that data to inform FDA submissions [5].

Stated-preference methods are survey-based methodologies for valuation of a non-market good, a characteristic that makes them particularly useful for PCBR assessment [9-10]. They contrast revealed preferences studies that determine value based on observed behavior [10-11]. Discrete-choice experiments (DCE) and best-worst scaling (BWS), two commonly used stated-preference methods in healthcare [12-14], require respondents to choose among hypothetical alternatives. Under the assumption that the respondents' choice maximizes their utility, comparison of choices across multiple combinations of attributes and levels are used to calculate the relative utility for a particular attribute [10,15]. Thus, the appropriate specification of attributes and levels are necessary for a valid instrument.

Attribute development for a stated-preference survey is generally conducted as a two-staged process consisting of conceptual development and refinement [16]. Conceptual development considers the list of attributes that inform the benefit-risk tradeoff and refinement translates those attributes to lay audiences [16]. The importance of systematic and transparent methods for attribute development in stated-preference methods is well documented [16,17]. While experts suggest incorporating community members to support attribute refinement, there has been little guidance on how to conduct and use evidence generated from such interactions [8,18]. Furthermore, lack of transparency about attribute development leaves researchers with few models to follow and less clarity in interpreting results [16,19-20]. There is a growing body of literature that uses consensus methods for attribute development, but this focuses on reducing long attribute lists to a manageable number in the conceptual development stage [21-24]. Consensus methods techniques are not ideal for attribute refinement or in a pragmatic, rapid context. The limited available guidance suggests using qualitative methods for attribute development [16, 25-26], but only one reports a development methodology [27].

We describe a community-engaged process for study design in the Duchenne and

Becker muscular dystrophy (DBMD) community. DBMD is a rare, neuromuscular disease characterized primarily by muscle degeneration resulting in weakness, loss of ambulation, and premature death [28]. We focus on attribute refinement for a preference study designed to inform regulatory review for a therapeutic agent that demonstrated pulmonary benefits in phase III trial results. Previous research demonstrates the community's willingness to accept risk for slowing the progression of muscle weakness [29], the hallmark characteristic of DBMD, but no data existed on preferences for pulmonary benefits. Pulmonary-focused therapeutic targets are appealing to clinicians because deterioration in pulmonary function is one of the primary causes of death [30-34].

The aim was to test a community-engaged process for stated-preference survey development to inform regulatory benefit-risk assessment. This context requires an approach that is both pragmatic and rapid. The purpose of this paper is to describe our context-specific approach and illustrate its use designing stated-preference instruments to aid regulatory benefit-risk assessment.

3.3 Methods

Process overview

We describe a community-engaged process to inform the design of a stated-preference study and tested that approach for patients and caregivers of people with DBMD (see Figure 3.1). Because this effort occurred in direct response to regulatory guidance documents, an industry sponsor initiated the process by approaching an advocacy organization to lead a scientific team. The advocacy organization organized a scientific team with relevant expertise. First, the scientific team developed a set of guiding principles with foundations in the principles of community-engaged research [35]. Next, appropriate sources of stakeholder variety were identified and volunteers were purposefully recruited to represent diverse perspectives. Sufficient stakeholder variability was particularly important because the survey targeted three populations included teens and adults with DBMD and caregivers. The clinician perspective was also valued given their role in facilitating treatment choice. Thus participating stakeholders included adults with DBMD, caregivers of children of

diverse ages, and clinicians. The trial sponsor, who funded the survey development, was also included, with similar influence on attribute development as other stakeholders involved in the process. A committee structure was established to organize stakeholders around specific project goals. In addition to the scientific team, there were leadership, stakeholder and review committees, which are described in detail below. Finally, the scientific team defined the relevant outputs of each committee based on how outputs would translate to desired outcomes and ultimate impact. The goals of engagement were to inform survey design such that the survey was ethical and acceptable, meaningful to the community, and produced quality patient-centered benefit-risk data. The overall impact of engagement and the survey was to identify patient and caregiver priorities regarding therapeutic targets and enhance regulatory review with PCBR.

Guiding principles

As shown in Figure 3.1, the guiding principles were: 1) incorporating patient perspectives into drug development and regulatory review is worthwhile; 2) patient and caregiver perceptions of meaningful benefits/risks may differ from researcher and clinician perspectives; 3) the patient and caregiver community is actively engaged and willing to participate; 4) study data belong to the patient and caregiver community; 5) all stakeholders deserve a voice in study development; and 5) regulators are receptive to preference data.

Committee structure and goals

A leadership committee guided the entire project and reviewed all major decisions informed by interactions with other stakeholders. This included advising on inclusion and exclusion criteria, informing conceptual survey development and subsequent refinement, and addressing concerns during development. The leadership committee participated in one-on-one and group calls, and subsequently provided input through email and in-person communications. They continue to advise on advocacy implications of the findings and results dissemination.

The scientific team was a subset of the leadership team that executed the project. Although all the committees were vital to the development process, the

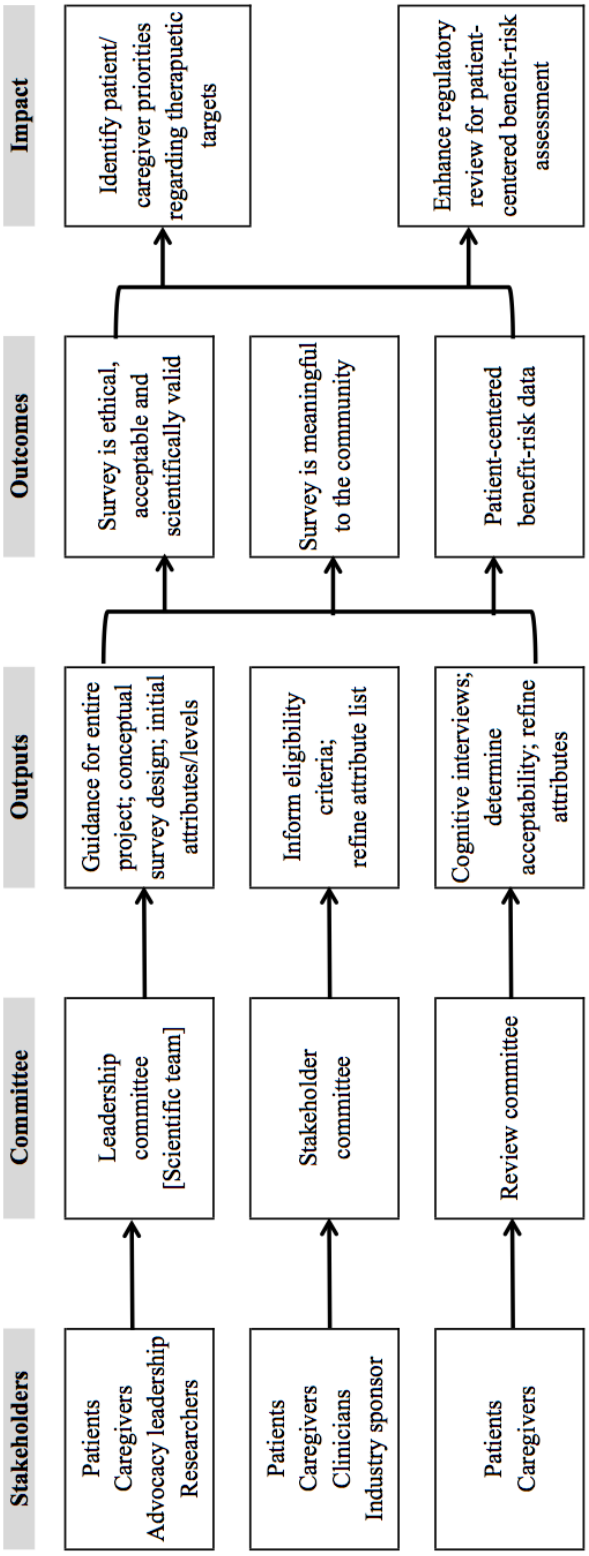

Figure 3.1: Community engagement process and outcomes for stated-preference attribute development.

scientific team was responsible for synthesizing information, making scientific decisions, and confirming those decisions with the leadership team. Although informed by the various committees, the scientific team ultimately was responsible for the scientific integrity of the study. This information flow allowed for flexibility so that all stakeholders could be responsive to emerging needs.

The stakeholder committee contributed to creating and refining a pool of potential treatment attributes and levels, as well as the survey language that introduced the experiments and the attributes. Members were asked to participate in either one-on-one or group meetings or conference calls. They also provided written feedback on the attribute list and responded ad hoc to questions during survey development. Clinician and patient/caregiver interactions were conducted separately to address slightly different topics. Clinician participants were asked how they would describe the potential benefits and risks/burden of the therapy to their patients based on the phase III trial data, and then to discuss non-skeletal muscle DBMD symptoms that patients may find important as therapeutic targets. Patients and parents were asked about their perceptions of the potential benefits and potential risks or burdens of the therapies, and then discussed DBMD symptoms that should be prioritized as treatment targets. The conversations continued to discuss how these may be incorporated into a survey to explore the meaningfulness of the pulmonary benefits and how to frame risks and burdens.

Leadership and stakeholder committee members were provided with detailed scientific reports and a lay summary of the clinical trial results. The trial was discussed at the beginning of the first engagement. Finally, the leadership and stakeholder committees each discussed ethical determination of inclusion criteria, focused on a balance between allowing the broadest inclusion possible versus defining appropriate age cutoffs for a survey that includes emotionally-laden content. The leadership and stakeholder committees comprised adults with DBMD, caregivers, advocacy organization leadership, clinicians and a industry sponsor representative.

The review committee participated in cognitive interviews to refine the instrument. The review committee consisted of eligible survey respondents: caregivers of people with DBMD and adults with DBMD. During the cognitive interviews,

committee members completed the draft survey while reading aloud and sharing stream-of-conscious reactions. Prior to each interview the scientific team identified priority areas for input, such as potentially confusing directions, item wording, and emotionally difficult sections. These interviews took place over Skype, a pragmatic choice for a rare disease population that allowed the research team to benefit from visual cues. All interviews were audio recorded and reviewed by two team members. After the interviews, review committee members were asked to review survey changes that resulted from their participation for final input and suggest appropriate ages for survey eligibility. An iterative approach to survey design was used such that learnings from each interview were applied to the most current version of the survey. Following the cognitive interviews, ad-hoc advice was sought from stakeholder committee members to inform final survey language.

3.4 Results

Participants and activities

Final committee membership included 20 individuals across three committees. The leadership committee (n=6) included a researcher with stated-preference method expertise (n=1), advocacy organization members including leadership and community-engagement experts (n=3), an adult with DBMD (n=1) and a parent (n=1). The stakeholder committee (n=8) included parents (n=2), adults with DBMD (n=2), clinicians (n=3) and an industry representative (n=1). Review committee members (n=6) included adults with DBMD (n=3) and parents (n=3). Each committee member served on only one committee.

Committee members represented a diverse age range of people affected by DBMD, though all were affected with DMD (none with BMD). Parent committee members were all mothers and had at least one child with DBMD ranging from age 5 to 22 years. Clinician members were physicians of rehabilitative medicine or neurology (n=2) and an advanced practice nurse (n=1).

Engagement activities entailed over 15 hours of formal engagement including 15 interviews and recorded conference calls. These formal engagement efforts were augmented with in-person conversations and email communications, with most

stakeholders receiving at least two additional email and/or in-person requests for additional input. Stakeholder committee members participated in one of six meetings of average 46 minutes (range 38-55 minutes) to discuss potential attributes and whether they perceived them to be meaningful. Additionally, we conducted six cognitive interviews with review committee members that were on average 67 minutes (range 52-112 minutes) and iterated on three versions of the survey that included about 50 detailed wording iterations. Details of committee membership and interactions are outlined in Table 3.1.

Committee	Objective	Members include	Interactions
Leadership committee (n=6)	Guided entire project; Conceptual survey design; Developed initial attribute/levels	Adult with DBMD (n=1) Mother (n=1) Advocacy leadership (n=3) Researcher (n=1)	Continuous feedback loops via one-on-one interactions, group conference calls, and email communication
Stakeholder committee (n=8)	Advised attribute refinement; Informed eligibility criteria	Adults with DBMD (n=2) Mothers (n=2) Physicians (n=2) Advanced practice nurse (n=1) Industry representative (n=1)	6 meetings Mean length: 46 min (range: 38-55 min)
Review committee (n=6)	Cognitive interviews to determine acceptability and refine attributes	Adults with DBMD (n=3) Mothers (n=3)	6 interviews Mean length: 67 min (range: 52-112 min)

Table 3.1: Committee membership and resulting interactions from community-engagement.

Engagement goals

Study inclusion criteria

Stakeholders were critical in helping to make ethical choices about study inclusion criteria. The scientific team aimed to balance an obligation to allow as many participants as possible with concerns about potential negative psychological impacts of participation. We originally intended to include caregivers of children age 5 and above. Stakeholders contributed to an improved understanding of the psychological impact of the experiment. After a review committee participant with a young child experienced emotional upset during the survey, the committees explored the implications of a survey about pulmonary decline, which is a later-onset manifestation of DBMD, for parents of young children. This led to further consideration of participant protection and the potential for scenario rejection, resulting in changing

the inclusion criteria for parents to those whose child was at least 10 years of age. Similarly, based on feedback from the adult stakeholders with DMD, we raised the minimum age for teenage participation from 10 to 14 years.

Survey design

Consistent with best practices, the scientific team did not finalize the survey design until after the community considered the attributes. The research team originally proposed a DCE to measure treatment preferences for benefits and risks, but as it became clear that the survey would include two attributes related to pulmonary outcomes, the scientific team felt that a BWS case 2, which focuses on choices among attributes within a profile, would be more productive than DCE, which focuses on choices among profiles. This allowed for greater differentiation between the two pulmonary attributes. Similarly, the experimental design originally included six attributes with three levels each. Engagement efforts elucidated that there were two core, meaningful benefit attributes that reflected but did not significantly overstate the potential benefits of the drug. Engagement also reinforced stakeholders' overall desire to reduce complexity. Thus, to minimize respondent burden and in the interest of facilitating the participation of teenage respondents, an abbreviated version of the BWS case 2 experiment included only four attributes (cough strength, chance of lung infections, chance for diarrhea and need for additional blood tests). Finally, stakeholders reinforced the importance of incorporating an "intention to use" question for each treatment profile, similar to an approach previously used by our group [36].

Based on a desire to maximize the impact of the study on the entire drug development process, the final survey also included an exploratory BWS case 1 experiment of 11 attributes (five per task) to measure respondent's priorities for non-skeletal muscle DBMD signs and symptoms as treatment targets. Stakeholders selected weaker ability to cough, lung infections, weaker heart pumping, frequent waking at night, bone fractures, constipation, headaches, feeling tired, non-healthy weight, poor attention span and depression. These objects and definitions are shown in Table 3.2. As previously described, these items emerged from the leadership and stakeholder committee processes. Based primarily upon request from the

sponsor and with support from the leadership committee, a third section comprising a series of six Likert-type questions was added to describe additional benefit and burden variables of interest. The final version of the attributes and levels used in the survey can be found in Table 3.3.

Final objects and definitions used for BWS case 1 experiment
1 Weaker ability to cough DBMD progression results in decline in respiratory function and the ability to cough forcefully, making it harder to clear the airway and breath deeply. Sometimes assistive devices are used.
2 Lung infections Lung infections require doctor visits and taking antibiotics. Serious infections like pneumonia have to be treated in the hospital and might make it harder for the lungs to work well over time.
3 Weaker heart pumping Over time, people with DBMD experience weaker heart pumping and have to take heart medication.
4 Frequent waking at night Teens and adults with DBMD may have more trouble sleeping soundly through the night, partly due to decline in lung function. This may require help from caregivers to sleep comfortably.
5 Bone fractures Loss of ambulation and steroid use can contribute to weakened bones, which leads to an increased risk of fractures.
6 Constipation Immobility or medication side-effects results in people with DBMD having trouble with constipation (going more than 2 days without a bowel movement).
7 Headaches Poor respiratory functioning in teens and adults with DBMD may cause them to experience frequent bad headaches.
8 Feeling tired People with DBMD may have trouble with feeling tired after they wake-up and throughout the day (also known as "daytime sleepiness").
9 Non-healthy weight People with DBMD can have trouble maintaining their weight (some may have trouble gaining enough weight, while others have the problem of gaining too much weight).
10 Poor attention span Some people with DBMD experience more problems with paying attention and staying focused on a task than other people.
11 Depression Living with DBMD may increase the chance for symptoms of depression, such as feeling sad, irritable, or not being interested in activities.

Table 3.2: Refined objects and definitions for BWS case 1 experiment.

Attribute refinement

Community engagement was vital to informing the presentation of pulmonary benefits, for two reasons. First, though pulmonary decline is ubiquitous as Duchenne progresses and contributes substantially to morbidity and mortality, pulmonary decline is asymptomatic or associated with diffuse symptoms for a significant portion of affected individual's lives, making the identification of meaningful attributes more challenging [30-34]. As a result, clinician, patient and caregiver stakeholders

Cough Strength
Taking the medicine may help slow the impact of DBMD on the ability to cough. A weak cough is part of the progression of DBMD as people get older and their lung function gets worse. A strong cough is important for clearing the airway and letting you get a good deep breath. Here are the ways the medicine could help your ability to cough:
Maintained for up to 10 years
This means that your cough would stay as strong as it is now for an average of 10 more years. If you have no trouble coughing well now, you won't have any trouble for about 10 more years. If you have mild trouble with coughing now, it will not get worse for about 10 more years. If you have a weak cough now, it will not get worse for about 10 more years.
Maintained for 2 years
This means that your cough would stay at the current level for an average of 2 more years.
No benefit
The drug would not work on your coughing at all, so your cough would weaken over time.
Lung Infections
Taking the medicine may help you get fewer infections in his lungs. Getting an infection in the lungs means you have to go to the doctor and take antibiotics. Serious infections like pneumonia have to be treated in the hospital, and they might make it harder for your lungs to work well over time. Here are ways that the medicine could help with lung infections:
Very few
After you start taking the drug, you would get lung infections very rarely, if at all, for your whole life.
Half as many
After you start taking the drug, you would get about half as many lung infections compared to if you did not take the drug.
No benefit
The drug would not affect how often you get lung infections.
Mild Diarrhea
Because of taking the medicine you may get mild diarrhea. This means that you have 2 to 4 more bowel movements a day, but you do not have to go to a doctor for it. The diarrhea may last only a few days. Taking the medicine may cause:
0%
No (or 0%) extra chance you will get diarrhea.
20%
1 out of 5 (or 20%) chance you will get diarrhea.
50%
1 out of 2 (or 50%) chance you will get diarrhea.
Blood Tests
Because of taking the medicine, for the whole time you are treated you will have to have blood tests for safety. Your doctor may ask for:
No blood rests
No blood tests. This means you do not have to have any extra blood tests during the year.
Blood tests 2 times a year
This means you have extra blood tests every 6 months
Blood tests 4 times a year
This means that you have extra blood tests every 3 months

Table 3.3: Refined attributes and levels for BWS case 2 experiment.

agreed that most patients view lung function as important but may feel limited immediacy for this outcome, especially at younger ages. Similarly, adults with DMD had difficulty conceptualizing how a pulmonary benefit might affect their activities of daily living. Thus, though all agreed that pulmonary benefits would be seen as important, they acknowledged the hidden nature of pulmonary benefits and agreed that the attributes would be more meaningful if tied to "visible" outcomes of pulmonary function. Pulmonary benefits of interest were potential patient-relevant downstream benefits such as daytime fatigue, sleep quality, headaches, and mortality; clinician and advocacy advisors, however, cautioned that they would not describe such benefits to their patients without additional data on the therapeutic effects. This reflects the inherent tension between the pulmonary benefit used in the clinical trial (upon which the study was based) and the benefits important to patients and families. To achieve our goals, it was vital that we developed meaningful attributes that were as consistent with the trial benefits as possible, while remaining understandable and accessible to those in the DBMD community.

Thus, our engagement process determined that the survey would not include a global pulmonary attribute or a functional measurement such as peak expiatory flow (PEF) or forced vital capacity (FVC), which were the clinical trial outcomes. Though not primary endpoints, the clinical trial did measure number of respiratory infections and cough strength. These were considered to be meaningful to our stakeholders, even for patients and parents who could not yet clearly anticipate how such benefits would impact their day-to-day lives. Frequency of lung infections and slowing the decline of cough strength were the benefits ultimately used in the survey. The specific wording of the attribute levels and the instruction set were also developed in collaboration with our stakeholder groups.

3.5 Discussion

We present a community engagement process and demonstrate its use for stated-preference survey design. We offer a pragmatic, cost and time-permissive engagement process to guide attribute development that is not in conflict with the qualitative research employed by other researchers in choice survey development [17, 37-38]. Using the classification system used to evaluate community engagement

strategies in Clinical and Translational Science Award (CTSA) program applications [39], our process meets the criteria for designation as "high-input" from the community. Furthermore, our process has similarities with the FDA's process for developing patient-reported outcomes (PRO) measures [40]. Both processes are iterative, focus on content validity, and begin with conceptual development by a scientific team and use patient input to adjust and refine [40].

A key element to understanding the community, its constituents and its capabilities was the collaboration between research and advocacy organizations. The study was co-led by advocacy and academic institutions, with support from the trial sponsor. The collaborative scientific team included experts in the use of stated preferences at Johns Hopkins University and PPMD, a team that has demonstrated leadership and influence in the movement towards PCBR assessment in regulatory decision-making and community-engagement expertise [29,4]. PPMD is also an organization working solely to advance the needs of the DBMD community and therefore its team members have condition-specific knowledge and a deep understanding of their community [35]. The scientific team previously conducted engagement together, which allowed these efforts to be viewed as part of an evolutionary process and build off of previous efforts [4,29,36,41]. Partnerships with organizations less entrenched in the disorder community of interest, and/or with limited engagement experience may require guidance about and more time to conduct this process, which underscores the importance of this work as an exemplar.

A limitation of our engagement was that all committee members had DMD, leaving BMD under-represented. However, these are related disorders with symptomatic overlap, and our committee members represented diversity in symptomatology and progression. Similarly, all of our caregivers were mothers. The absence of fathers reflects the common bias of mothers as caregivers for children with pediatric onset disorders and as participants and targets of caregiver research in Duchenne [41-44]. The presence of fathers is not likely to alter the results because the goal of engagement was not consensus regarding survey attributes for inclusion, but aimed to optimize attribute presentation, which is not expected to differ for fathers. Interpretation differences would likely be confounded with caregiver-burden, in which case factors other than sex are more influential such as parental experience, patient

functional status, psychological outcomes, and coping styles [44-46]. We aimed to engage a variety of parents in terms of influencing factors where appropriate.

A limitation of this approach is that, while the process is transferrable, the specific engagement must be tailored to each stated-preference study. Due to the time-intensive nature of these activities, it may be useful to conduct them concurrently with other regulatory review preparations to avoid extending the drug development timeline. The risk of repeated demands on the community is also of concern, particularly for rare diseases with smaller communities. Repeated use of the same motivated participants puts them at risk for burn out. This risk can be reduced by ensuring engagement activities serve as a source of empowerment for community-members by communicating the meaningful impact on research and enabling considerations of real-life decision-making scenarios they might face in the future [35].

Engagement activities led to concrete changes to the study, such as a re-evaluation of the overall experimental design, both in terms of the type of choice tasks and the number of attributes. Therefore, it is important that engagement be conducted in iterative, cyclical stages rather than consecutive stages to best inform the survey design. This is consistent with the key principles of other engagement frameworks [47]. Using information gained from engagement, we opted for a BWS design, despite the fact that DCE has the advantage of having the ability to calculate maximum acceptable risk.

In this example, the scientific team had a clear directive to determine how the community views the benefits and risks associated with a potential pulmonary therapeutic and we worked to engage the community within those parameters. This necessitated that one attribute be related to pulmonary benefit and the other benefits and risks to be of similar range for the experiment to be able to meet the study goals. Engagement helped to define other tangible benefits that were considered to be meaningful on a similar scale. The underlying assumptions of choice methods require that no attribute dominate the others so that there are observable trade-offs [48]. For instance, including a significant skeletal muscle benefit may have caused the experiment to fail because it would likely have dominated the other potential benefits.

Trial sponsors and the FDA operate within a research culture that shapes their beliefs and understanding of health and illness in terms of measurable clinical endpoints. An essential part of community engagement is to strive to understand the patient's point of view and how it shapes understanding of health and illness [35]. For instance, engagement highlighted that the natural history of the disease is such that many people do not experience obvious respiratory symptoms until later stages of disease and therefore the community felt disconnected from the clinical trial endpoint. Engagement prevented imposing a research cultural context onto the community, which ultimately improves the research impact by ensuring relevancy and expediting translation into practice.

The gains from engagement can apply to the broader drug development landscape as well. For instance, our BWS case 1 experiment asks respondents to prioritize the aspects of the disease they would most prefer drugs to address. This information can be used by sponsors developing the next generation of therapies, or by priority-setting funding agencies. This information would also be useful to determine relevant patient-centered outcomes as secondary clinical trial endpoints. Furthermore, quantifiable risk tolerance information such as that provided in our BWS case 2 experiment may also inform future research directions rather than relying on assumptions about what level of risk patients and caregivers are willing to accept.

3.6 Conclusions

This study describes a process for developing a stated-preference survey for patient-centered benefit-risk assessment within the context of an existing therapeutic agent after clinical trial. We demonstrate that a community-engaged approach can incorporate community members as varied as adult patients, caregivers, clinicians, clinical trial sponsors, and professional advocates who can contribute important information to the survey design. We established that community engagement enhances the process of attribute refinement for patient-centered drug development, a context in which the goal is to understand patient priorities and preferences.

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Chapter 4

Caregiver and Patient Preferences of Treatment Targets: An Example for Duchenne and Becker Muscular Dystrophy Using Latent Class Analysis

[1]

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4.1 Abstract

Background Patient preferences are increasingly considered important for regulatory decision-making, but less attention has been given to their use in earlier stages of drug development or for building a body of preference knowledge. The primary objective of this study was to quantify patient and caregiver priorities for therapeutic targets in Duchenne and Becker muscular dystrophy. The secondary objective was to explore heterogeneity.

Methods This study utilizes a best-worst scaling case 1 experiment to elicit treatment priorities for 11 symptoms. Priority scores were calculated using conditional logistic regression for the aggregate sample and stratified by caregivers and patients. A two-class latent class analysis identified segments of the sample with differing preferences.

Results Results indicate that respondents in aggregate prioritize "weaker heart pumping" ($score = 4.67; 95\%CI = [4.22, 5.12]$) and pulmonary symptoms: "lung infections" ($score = 3.82; 95\%CI = [3.39, 4.24]$) and "weaker ability to cough" ($score = 3.45; 95\%CI = [3.05, 3.85]$) as the most important intervention targets and "poor attention span" as the least important intervention target (omitted category). There were no significant differences between caregivers and patients ($p - value = 0.14$), but at least two classes exist with different priorities. Priorities of the majority class (80%) are reflective of the aggregate results, whereas the minority class (20%) considers "weaker heart pumping" ($score = 2.84; 95\%CI = [2.35, 3.33]$) as more important than "weaker ability to cough" ($score = 1.67; 95\%CI = [1.11, 2.23]$) and "lung infections" ($score = 1.58; 95\%CI = [1.06, 2.09]$). Minority class membership was associated with ambulation ($OR = 6.166, SE = 5.23$) and inversely associated with use of cough assistive devices ($OR = 0.027; SE = 0.03$), indicating less advanced disease.

Conclusions Estimates of the relative importance for therapeutic targets for Duchenne muscular dystrophy indicate that symptoms related to quality-of-life and with direct links to morbidity and mortality are prioritized above other quality-of-life measures. Findings also suggest the existence of preference heterogeneity for treatment targets, which may be related to symptom experience.

4.2 Background

The muscular dystrophies (MD) are a group of muscle diseases characterized by progressive muscle loss and shortened lifespan [1]. Duchenne muscular dystrophy (DMD) is the most common and most severe form. DMD is a rare, genetic disease occurring in 1 in 5,000 live male births [2,3]. The average age of diagnosis is five years old, although boys usually begin to exhibit signs and symptoms in their toddler years when they begin to walk [4,5]. Loss of ambulation usually occurs in the early teen years. In addition to orthopedic symptoms, muscle loss leads to respiratory and cardiovascular complications. Cardiomyopathy and respiratory complications are the leading causes of death, which on average occurs at age 30 [4]. Becker muscular dystrophy (BMD) has similar characteristics to DMD, but is often milder and with slower progression [1]. There are currently no approved treatments for Duchenne and Becker muscular dystrophy (DBMD) and the standard of care relies on the off-label use of corticosteroids that have been shown to delay loss of muscle and delay complications [4].

Recognizing that science may be years from a drug that targets the underlying genetic defect for Duchenne and Becker muscular dystrophy (DBMD), the neuromuscular community is supportive of concurrent drug development efforts that aim to preserve quality-of-life for those with DBMD [6]. The current drug development pipeline includes drugs that target signs and symptoms of DBMD including muscle strength and function and cough strength. Previous research demonstrates caregiver preference for progressive loss of muscle function, a major quality-of-life issue, over life-extending interventions [7,8]. It is unknown which other signs and symptoms of DBMD that reduce quality-of-life are desirable targets for intervention.

Drug discovery programs are often initiated due to lack of available treatment options. Initial research includes developing a hypothesis for how a hypothetical therapy can alter a disease pathway and a target is selected [9]. Other factors for consideration in choosing targets include commercialization, profitability, and potential for discoveries to have spillover effects for other diseases. There is little evidence of substantial effort to adequately account for patient preferences when identifying therapeutic targets. Awareness regarding the importance of quantitative patient preferences in other aspects of drug development has increased in

recent years. The FDA has developed guidance documents for industry on how to incorporate these data into regulatory submissions [10,11]. The focus to date on quantitative preference data has primarily been with regard to the regulatory review process, and earlier stages of development are absent from the discussion [12-15]. One exception comes from the Medical Device Innovation Consortium (MDIC), a public-private partnership aimed at advancing regulatory science around the development and approval of medical devices. This group has developed a framework for incorporating patient preference information into the regulatory process [16]. As part of this framework MDIC identified opportunities for patient preference information to be collected and incorporated throughout the entire drug development lifecycle, such as building a body of patient preference knowledge that can be collected throughout the product lifecycle and contribute to regulatory review and post-market surveillance [16]. Specifically in the discovery and ideation phase, stakeholder input is relevant to understanding the areas of opportunity for therapy and pathways to addressing them.[16] Historically, this has relied heavily on qualitative data that has limited ability to reflect a variety of perspectives. Quantitative preference elicitation methods on the other hand can identify heterogeneity and there is a rapidly growing literature of examples of this in healthcare [17-30]. Quantitative data can be useful in framing benefit-risk issues, defining subpopulations and serving a role further down the line in developing clinical endpoints for trials.

Using DBMD as an example, this study demonstrates an empirical approach to building a body of knowledge of quantitative preference information that can be used in early phases of drug development and can assess preference heterogeneity among patients with the same disease. The primary objective of this study was to directly elicit patient and caregiver priorities for therapeutic targets for the signs and symptoms of Duchenne and Becker muscular dystrophy. The secondary objective was to explore heterogeneity of treatment priorities.

4.3 Methods

Survey development

This survey was developed using a community-engaged research approach so that patients and caregivers, as well as other key stakeholders, informed the survey design. Twenty stakeholders were involved in defining eligibility criteria, refining attributes, and determining overall relevancy. This ensured that the survey and list of attributes were meaningful to the community. In-depth details about the community-engaged approach are available elsewhere (see Chapter 3).

Survey methods

Best-worst scaling (BWS) is a choice-based preference elicitation method used to elicit preferences for various objects or attributes. Introduced in 1992 and with its formal theoretical and statistical properties proven in 2005, it has become increasingly popular in healthcare as an alternative to rating scales [31-34]. BWS is a form of conjoint analysis that presents survey respondents with a set of items from which the respondent identified the best and worst. There are three cases of BWS: the object case (case 1), the profile case (case 2), and the multi-profile case (case 3). In case 1, the respondent chooses the best and worst objects among a list of objects. In case 2, the respondent chooses the best and worst attributes and various levels of that attribute from among a hypothetical profile. Finally, in case 3, respondents choose the best and worst profiles from among a set of multiple profiles. Complete theoretical explanations and examples of healthcare applications for all three cases are available elsewhere [35,36]. In all three cases, the choices resulting from consideration of multiple questions are analyzed together to estimate relative importance.

Survey design

The final survey included a BWS case 1 experiment. This is an appropriate design for determining the relative value of a list of objects [36]. In this study, there were 11 objects defined as signs and symptoms of DBMD that are potential targets of therapeutic interventions. The list of objects were: weaker ability to cough, lung

infections, weaker heart pumping, frequent waking at night, bone fractures, constipation, headaches, feeling tired, non-healthy weight, poor attention span and depression. Additional details about the definition for each object are described in Table 4.1. Choice tasks were precipitated by a series of demographic questions about the survey respondent, questions about the clinical status of the individual affected with DBMD, and an introductory section that provided a brief definition of each sign or symptom and then answered a question about their own experience with that sign or symptom. For instance, after a brief definition of "lung infections" caregiver respondents were asked "Has your child with DBMD ever been treated for pneumonia" These salience questions were intended to pace the respondent's reading of the material and ensure the information was absorbed. It also provided data for exploring the relationship between experiences with symptoms and preferences to target those symptoms. Respondents were also presented with an example choice task to familiarize themselves with the experiment.

The objects were presented in 11 different choice tasks that each presented a sub-set of five objects. An example choice task is presented in Figure 4.1. A balanced-incomplete experimental design was used so that each object occurred the same number of times and co-occurred with other attributes equally. The design also had Youden design properties, which ensures that every object appeared in the same position the same number of times (once) [37,38]. This prevents the respondent from attributing importance to objects based on the composition of the choice task [36]. Respondents were asked to evaluate the five objects and choose the object that he or she considered the most important to treat and the object that he or she considered the least important to treat. The design was identified from the SAS database of orthogonal arrays [39]. The survey was administered online using Qualtrics.

Most important to treat		Least important to treat
O	Frequent waking at night	O
O	Headaches	O
O	Feeling tired	O
O	Weaker ability to cough	O
O	Constipation	O

Figure 4.1: Sample BWS task used to elicit relative preferences for signs and symptoms as therapeutic targets.

Objects	Definitions
1	**Weaker ability to cough** DBMD progression results in decline in respiratory function and the ability to cough forcefully, making it harder to clear the airway and breath deeply. Sometimes assistive devices are used.
2	**Lung infections** Lung infenctions require doctor visits and taking antibiotics. Serious infections like pneumonia have to be treated in the hospital and might make it harder for the lungs to work well over time.
3	**Weaker heart pumping** Over time, people with DBMD experience weaker heart pumping and have to take heart medication.
4	**Frequent waking at night** Teens and adults with DBMD may have more trouble sleeping soundly through the night, partly due to decline in lung function. This may require help from caregivers to sleep comfortably.
5	**Bone fractures** Loss of ambulation and steroid use can contribute to weakened bones, which leads to an increased risk of fractures.
6	**Constipation** Immobility or medicaiton side-effects results in people with DBMD having trouble with constipation (going more than 2 days without a bowel movement).
7	**Headaches** Poor respiratory functioning in teens and adults with DBMD may cause them to experience frequent bad headaches.
8	**Feeling tired** People with DBMD may have trouble with feeling tired after they wake-up and throughout the day (also known as “daytime sleepiness”).
9	**Non-healthy weight** People with DBMD can have trouble maintaining their weight (some may have trouble gaining enough weight, while others have the problem of gaining too much weight).
10	**Poor attention span** Some people with DBMD experience more problems with paying attention and staying focused on a task than other people.
11	**Depression** Living with DBMD may increase the chance for symptoms of depression, such as feeling sad, irritable, or not being interested in activities.

Table 4.1: Signs and symptoms of DBMD included as objects in the BWS case 1 experiment.

Recruitment and sample

The intended respondents were patients with Duchenne or Becker muscular dystrophy and caregivers of children with DBMD. A targeted recruitment strategy was used with the opportunity for supplemental snowball sampling. Potential respondents were recruited via flyers at an annual patient and family conference in June 2015. Two days following the conference, Parent Project Muscular Dystrophy (PPMD) sent emails to its DuchenneConnect registry participants who met the survey eligibility criteria. A follow-up email was sent to the same distribution list approximately one month later. Due to the difficulty in recruiting sufficient respondents in a rare disease community, the survey link was public, which afforded the opportunity for community members to invite other interested community members to participate. The survey was in the field for 5 weeks.

The inclusion criteria for caregiver survey respondents were that caregivers had to be at least 18 years of age and have at least one child with DBMD at least 10 years old. For patient respondents, the inclusion criteria were that he had to be living with Duchenne or Becker muscular dystrophy and at least 14 years of age. Only those living in the United States were eligible. The protocol for the study was approved by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (IRB # 00006299). All participants provided informed consent electronically.

Statistical analysis

Choice outcomes across all 11 tasks were used to estimate the relative values associated with objects. Responses were analyzed using sequential best-worst scaling. Conditional logistic regression models produced estimates for the aggregate sample. The dependent variable was the choice of an attribute as best or worst. The independent variables were 10 of the 11 available attributes. The attribute most often chosen as least important was used as the reference category. The estimates for the other 10 objects can be interpreted relative to the least important object. The survey did not allow a respondent to advance to the next choice task without answering the current task, therefore there were no missing data for the experiment. The data were analyzed using STATA 14 (StataCorp LP, College Station,

Texas).

Two secondary analyses were used to explore heterogeneity. First conditional logistic regression models were repeated for stratified samples of caregivers and patients. Overall models and individuals parameter estimates were compared using Wald tests. Second, we conducted a latent class analysis to explore potential sources of heterogeneity. The results of this analysis include each respondent's probability of class membership and class-specific parameter estimates. Classes were compared on the basis of demographic and clinical characteristics using t-tests for independent samples. The results of comparisons were used to construct a multivariate model with relevant covariates. Finally, logistic regression was used to identify associations between demographic and/or clinical characteristics and class membership. The outcome variable was minority class membership and the independent variables were diagnosis, ambulatory status, respondent type, income, and all of the 11 clinical characteristics associated with the signs and symptoms from the experiment (listed in Table 4.1).

4.4 Results

Study sample

The survey link was distributed on June 20, 2015. Of 323 recipients who opened the email invitation to participate, 93 clicked on the survey link (response rate: 29%). Additional people gained access to the survey through the aforementioned snowball strategy. The survey was closed on July 30, 2015 at which point the survey had been accessed 235 unique times. In 198 of those cases, the respondent met the inclusion criteria and provided informed consent (consent rate: 83%). The final sample of those who completed the BWS case 1 experiment included 155 participants (completion rate: 78%). Of the 43 that dropped out, most did so at the start of the experiment; 86% (n=37) did not answer the first choice task, 11% dropped out before the second task, and one respondent completed all but the final task. Information about non-responders is not available.

Table 4.2 summarizes the respondent characteristics. Of the 155 respondents, 62% were caregivers ($n = 96$) and 38% were patients ($n = 59$). The majority of

caregivers were 45 years or older (56%), which skewed the age distribution for the aggregate sample. Patient respondents were 22% under age 18, 49% 18-30 years, and 27% were over 30 years old. The majority of respondents were white (89%), with 8% Hispanic and 5% black. The majority of respondents reported annual household income greater than $50,000 (61%), and 19% that reported incomes greater than $100,000). Respondents were disproportionately located in the South (39%) and West (25%). The majority of caregiver respondents were married or in long-term relationships (73%), but only 15% of patient respondents were married. Of the caregiver respondents, an overwhelming majority were mothers (76%) and highly educated (58% college graduates).

	Respondents (n=155)	
	Frequency	Percent
Survey respondents		
Relationship to affected individual		
Mother	73	47%
Father	17	11%
Adoptive mother	5	3%
Grandmother	1	1%
Self (Patient)	59	38%
Age Categories		
30-39 years	13	8%
40-49 years	29	19%
50-59 years	49	32%
65+ years	63	41%
Race		
White	138	89%
Hispanic	13	8%
Native	5	3%
Black	7	5%
Asian	3	2%
Other	2	1%
Income		
<$50K	35	23%
$50-75K	31	20%
$75-100K	34	22%
>$100K	30	19%
Region		
Northeast	27	17%
Midwest	26	17%
South	60	39%
West	42	27%
Marital status		
Single	42	27%
Married/Long-term relationship	79	51%
Divorced/separated/widowed	19	12%
Highest level of education*		
High school	39	25% (41%)
College graduate	35	23% (36%)
Professional degree	21	14% (22%)
Not asked	59	38%

* indiciates question not asked for patient respondents- percentages in parenthesis reflect percentage based on caregiver population (n=96).
Note: Not all rows will add to 100% due to missing data not shown. Race categories are not mutually exclusive.

Table 4.2: Survey respondent demographic characteristics (n=155).

As shown in Table 4.3, the majority of affected individuals had Duchenne muscular dystrophy (85%), compared to 12% with Becker muscular dystrophy. Most affected individuals had some history of steroid use (77% had used them previously or currently) and a majority were non-ambulatory (63%), which was defined as being able to do some walking indoors, even if they need help to do so and required a wheelchair outdoors. Most respondents had either private health insurance coverage (43%) or a combination of private and public plans (37%). Reflective of the differences in eligibility criteria between caregivers and patients, and because there were more caregiver respondents than patient respondents, the age distribution for affected individuals age skewed young with 86% being 10-17 years old. The mean age of affected individuals among patient respondents was 27.5 years old ($SD = 14.1$). Additional details about experience with DBMD symptoms are available in Table 4.3.

Statistical results

Priority scores

Figure 4.2 compares the relative importance of the 11 potential therapeutic targets for the aggregate sample. The horizontal bars around each point estimate represent the 95% confidence interval (CI) of that estimate. The most important symptom to target was "weaker heart pumping" ($score = 4.67; 95\%CI = [4.22, 5.12]$), followed by "lung infections" ($score = 3.82; 95\%CI = [3.39, 4.24]$) and "weaker ability to cough" ($score = 3.45; 95\%CI = [3.05, 3.85]$). The confidence intervals for "weaker heart pumping" and "lung infections" overlap, but just barely, which indicates that respondents did not differentiate cardiac targets from pulmonary targets. The confidence intervals of the two pulmonary benefits ("lung infections" and "weaker ability to cough") overlap, indicating that respondents did not differentiate priorities between these two targets. All three of the most important targets do not have overlapping confidence intervals with any of the lower-ranked targets, indicating a strong prioritization for cardiac and pulmonary targets. The least important target was "poor attention span" and was used as the reference (omitted) object such that all other estimates can be viewed as relative to it. None of the confidence intervals for any of the targets overlap include zero, indicating that "poor attention span"

	Respondents (n=155)	
	Frequency	Percent
Age		
10-13 years	42	27%
14-17 years	44	28%
18-25 years	37	24%
25+ years	31	20%
Diagnosis		
Duchenne	132	85%
Becker	19	12%
Intermediate	3	2%
Ambulatory Status		
Ambulatory	56	36%
Non-ambulatory	98	63%
Steroid use		
Currently or previously	120	77%
Never	33	21%
Insurance		
Private	67	43%
Public	28	18%
Both	58	37%
Signs and symptoms		
Use of cough assist	78	50%
Treatment for pneumonia	41	26%
Use of cardiac medication	13	73%
Bone fractures	72	46%
Trouble sleeping		
Never/rarely	104	67%
Sometimes	27	17%
Often/always	21	14%
Bowel movement frequency		
Less than daily	69	45%
Daily	70	45%
More than daily	12	8%
Headaches		
Less than 2 per week	134	86%
More than 2 per week	14	9%
Fatigue		
Never/rarely	62	40%
Sometimes	65	42%
Often/always	26	17%
Weight		
Overweight	60	39%
Healthy	82	53%
Underweight	11	7%
Trouble concentrating		
Never/rarely	85	55%
Sometimes	42	27%
Often/always	26	17%
Depression		
Never/rarely	88	57%
Sometimes	54	35%
Often/always	10	6%

Note: Not all rows will add to 100% due to missing data not shown.

Table 4.3: Clinical characteristics and symptom experience of individuals affected with DBMD (n=155).

is significantly different from the other targets.

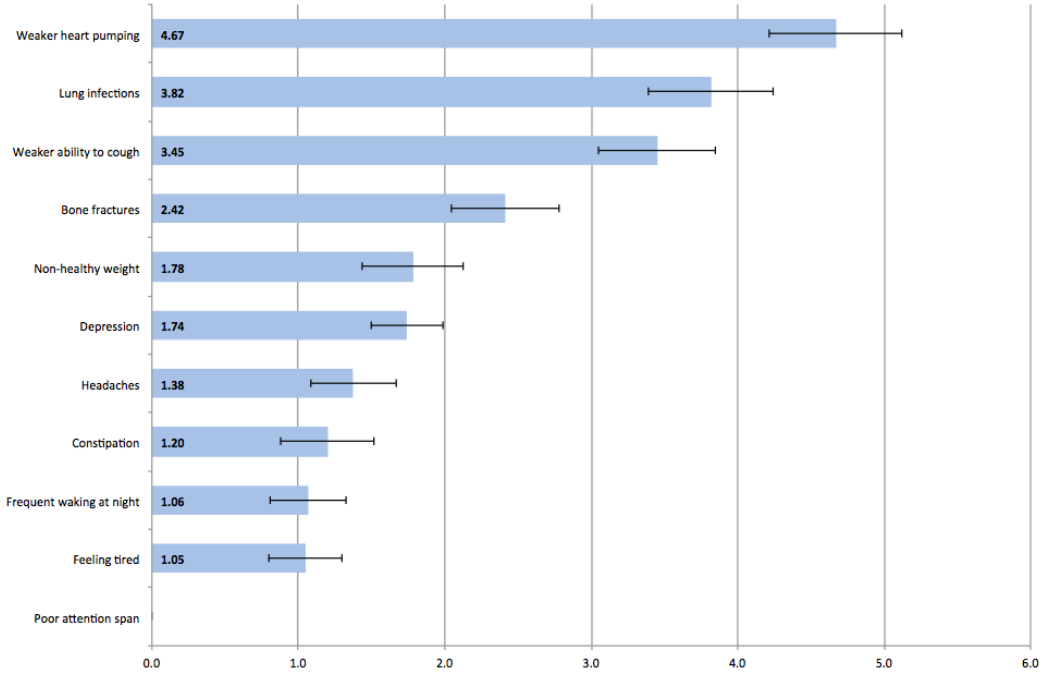

Figure 4.2: Caregiver and patient aggregate relative priorities for therapeutic targets.

The next most prioritized symptom was "bone fractures" ($score = 2.42, 95\%CI = [2.04, 2.78]$), although it overlapped with "non-healthy weight" ($score = 1.78; 95\%CI = [1.44, 2.22]$). The differences in relative importance for many of the middle-importance attributes were not statistically significant. The relative importance of "non-healthy weight", "depression", "headaches", and "constipation" were not distinguishable from one another based on overlapping confidence intervals. Although non-healthy weight and depression were barely overlapping with "constipation": "non-healthy weight" ($score = 1.78; 95\%CI = [1.44, 2.22]$) and "depression" ($score = 1.74; 95\%CI = [1.49, 1.99]$) vs. "constipation" ($score = 1.20; 95\%CI[0.88, 1.52]$). The relative importance of "headaches", "constipation", "frequent waking at night" and "feeling tired" were not significantly different.

Priority heterogeneity

A test between the caregiver and patient models indicates the overall models are not significantly different from one another ($p-value = 0.14$). (Data not shown). Furthermore, tests for differences between caregivers and patients for each individual attribute were not significant ($p-values > 0.05$). The priority scores for depression

were initially significantly different at the $alpha = 0.05$ level (1.99 for caregivers vs. 1.61 for patients; $p - value = 0.02$). However, once the Bonferroni correction was applied to account for multiple comparisons, the result was no longer significant. The relative preference order based on point estimates for some of the middle-ranked items differed between caregivers and patients. For caregivers depression was more important than non-healthy weight, whereas for patients the priority order of these two targets was reversed. Similarly, for caregivers headaches were more important than constipation, whereas for patients constipation was more important than headaches. However, overlapping confidence intervals between these attributes indicates no true differentiation within these groups of objects.

A latent class analysis was conducted to explore other potential sources of heterogeneity. Models for two classes up through 11 classes were evaluated for minimum AIC and BIC values to determine the optimal number of classes for the best-fitting model. However, model selection criteria were ultimately disregarded in favor of a 2-class model due to the small sample size [40]. For the 2-class model, 80% of respondents make up the majority class and 20% of the respondents make up a minority class.

As shown in Figure 4.3, the majority class reflected patterns similar to aggregate results and demonstrated greater prioritization for the three signs and symptoms that were prioritized in the aggregate analysis (cardiac and pulmonary symptoms). Like the aggregate results, the overlapping confidence intervals indicate no differentiation between "weaker heart pumping" ($score = 5.87; 95\%CI = [5.32, 6.42]$) and "lung infections" ($score = 5.08; 95\%CI = [4.53, 5.61]$) or "weaker ability to cough" ($score = 4.52; 95\%CI = [4.07, 4.97]$). For the minority class, "weaker heart pumping" ($score = 2.84; 95\%CI = [2.35, 3.33]$) was significantly different from the both pulmonary measures: "weaker ability to cough" ($score = 1.67; 95\%CI = [1.11, 2.23]$) and "lung infections" ($score = 1.58; 95\%CI = [1.06, 2.09]$). One difference between classes is that the minority class considered the two pulmonary benefits to be indistinguishable from "bone fractures", "feeling tired", "depression" and "non-healthy weight". Furthermore, "lung infections" was also indistinguishable from "headaches" in the minority class. Like the aggregate results, many of the middle attributes were not statistically significantly different from one another

within classes. One exception was that the minority class prioritized "feeling tired" ($score = 1.91; 95\%CI = [1.34, 2.48]$) above "frequent waking at night" ($score = 0.47; 95\%CI = [0.03, 0.91]$) and "headaches" ($score = 0.64; 95\%CI = [0.19, 1.09]$).

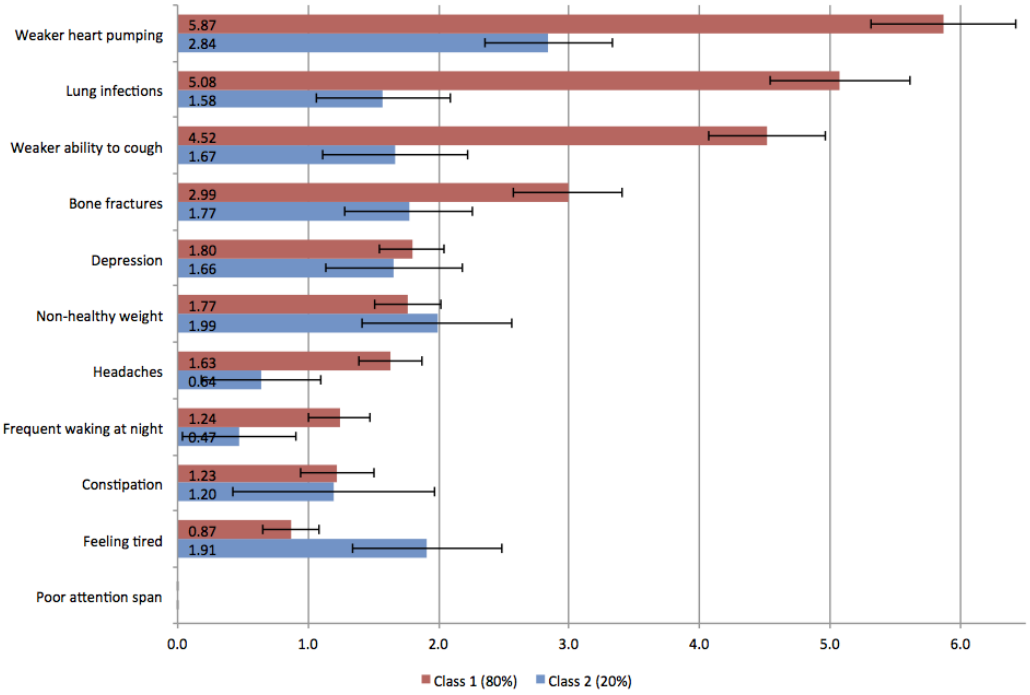

Figure 4.3: Caregiver and patient segmented (2-class) relative priorities for therapeutic targets.

Respondent type (caregivers and patients) was significantly different between classes, but did not perfectly predict class membership. Caregivers and patients made up 66% and 34% of the majority class, respectively and 45% and 55% of the minority class. Comparing the demographic and clinic characteristics of each class, we found no significant differences in diagnosis and ambulatory status between classes. In the majority class, a larger proportion of the affected individuals had Duchenne and a smaller proportion had Becker compared to the minority class (89% Duchenne and 10% Becker in majority class vs. 71% Duchenne and 19% Becker in minority class; $p - value = 0.04$). Ambulatory status also differed between classes. A much larger proportion (58%) of minority class respondents identified as ambulatory compared to majority class respondents (58% vs. 31%; $p - value = 0.01$).

The results of the logistic regression examining the association between demographic and clinical characteristics with minority class membership are presented

in Table 4.4. Minority class membership is associated with being ambulatory compared to non-ambulatory ($OR = 6.16; p - value = 0.03$), history of bone fractures compared to no history of bone fracture ($OR = 4.83; p - value = 0.04$), and occasional trouble sleeping compared to never or rarely having trouble sleeping ($OR = 13.79; p - value = 0.03$). Minority class membership is inversely associated with using cough assistive devices compared to not having used a device ($OR = 0.027; p - value = 0.01$), and frequent trouble concentrating compared to never or rarely having trouble concentrating ($OR = 0.031; p - value = 0.03$).

4.5 Discussion

In this study, we estimated the relative importance for therapeutic targets for Duchenne muscular dystrophy. Because there was little distinction between attributes among the top 3 attributes or between attributes of middle-level importance, results are best ordered according to four groups. Among an aggregate sample, cardiac ("weaker heart pumping") and pulmonary benefits ("lung infections" and "weaker ability to cough") were the most highly prioritized targets. "Bone fractures", "non-healthy weight" and "depression" were second most prioritized. The third group includes "headaches", "constipation", "frequent waking at night" and "feeling tired". All of above are desired targets of intervention more than "poor attention span". However, it warrants emphasizing that these are relative importance weights, and therefore none should be viewed as unimportant.

When two classes are distinguished, the minority class, although prioritizing cardiac symptoms above all else, considered pulmonary benefits to be undifferentiated from "bone fractures", "feeling tired", "depression" and "non-healthy weight". Feeling tired was prioritized higher among the minority class, making it fall into the second group, rather than the third.

Regression results comparing class membership and characteristics indicate a higher prioritization for signs and symptoms as treatment targets for which there is more experience with that target. "Bone fracture" was attributed greater relative importance in the minority group, a group in which those with history of bone fracture had 5 times greater odds of minority class membership. On the other hand, the minority class attributed less relative importance to pulmonary benefit;

	Odds Ratio	Std. Err.	P-value
Diagnosis (Ref: Duchenne)			
Becker	0.876	0.85	0.89
Intermediate	2.337	3.98	0.62
Ambulatory status (Ref: non-ambulatory)			
Ambulatory	6.166	5.23	0.03
Respondent type (Ref: caregivers)			
Patients	2.978	2.28	0.15
Income (Ref: <$50K)			
$50,001-75,000	0.275	0.36	0.32
$75,001-100,000	3.094	3.36	0.30
>$100,000	0.256	0.31	0.27
History of... (Ref: No history)			
Use of cough assist	0.027	0.03	0.01
Treatment for pneumonia	1.348	1.24	0.75
Use of cardiac medication	0.852	0.73	0.85
Bone fractures	4.825	3.78	0.04
Trouble sleeping (Ref: never)			
Sometimes	13.786	16.17	0.03
Often/always	0.197	0.41	0.44
Bowel movement frequency (Ref: daily)			
Less than daily	1.810	1.26	0.39
More than daily	3.928	5.08	0.29
Headaches (Ref: <2 per week)			
More than 2 per week	2.928	2.94	0.29
Fatigue (Ref: never/rarely)			
Sometimes	0.995	0.80	1.00
Frequent	4.218	5.16	0.24
Weight (Ref: healthy weight)			
Overweight	2.431	1.76	0.22
Underweight	1.996	3.46	0.69
Trouble concentrating (Ref: never/rarely)			
Sometimes	0.218	0.20	0.10
Often/Always	0.031	0.05	0.03
Depression (Ref: never/rarely)			
Sometimes	5.489	4.69	0.05
Often/Always	38.044	73.32	0.06

Ref = reference (omitted) category; Std. Err=standard error

Table 4.4: Logistic regression results for probability of minority class (20%) membership.

ambulatory respondents had 6 times greater odds of minority class membership. Similarly, those having used cough assistive devices had lower odds of minority class membership. This may indicate that the minority class has less advanced disease and that lack of experience with pulmonary symptoms may make it a less desirable treatment target. This result is consistent with qualitative community-engagement work we did in the survey development phase in which caregivers and patients had trouble relating to downstream pulmonary benefits which aren't experienced until later stages of disease progression (see Chapter 3).

Because these two models are estimated separately, and because this study discusses averages and not individuals, conclusive statements can not be made with regards to influential factors on individual-level preferences for treatment targets. However, we can conclude that preference heterogeneity does exist and should be accounted for in future research and needs assessment. This study indicates that preference heterogeneity may be particularly important among treatment targets related to quality-of-life. The most important target ("weaker heart pumping"), although also quality-of-life related, has an apparent, well-known link to morbidity and mortality. Therefore its prominence may be the reason there is consensus regarding its relative importance. Whereas, the targets of middle-priority are also related to quality-of-life, but lack as clear of a link to morbidity and mortality as the cardiac symptoms and may be influenced to a greater degree by past experience or current health status. Drug developers in needs assessment phases should consider quality-of-life targets.

A limitation of this work is that progressive loss of muscle function, the keystone characteristic of DBMD is not included in the list of potential treatment targets. Stopping and slowing the progressive loss of muscle has been shown to be very important to caregivers; results of a previous study of benefit-risk tradeoffs demonstrated a strong preference for slowing the progression of muscle weakness, even in the presence of a serious risk.[7] It was not included because this survey was developed in response to FDA guidance so that the data could be used as part of a regulatory review process for a drug with demonstrated pulmonary benefits in phase III clinical trials. As such, we were particularly interested in understanding preferences for pulmonary benefits.

4.6 Conclusions

We estimated the relative importance for therapeutic targets for Duchenne muscular dystrophy. Understanding the preferences of caregivers and patients has implications for drug development and regulatory decision-making. In summary, we found that on average respondents identified cardiac and pulmonary symptoms as the most important symptom to target with no differentiation between the two. Although we did not find differences between caregivers and patients, we did find that there are at least 2 classes of respondents with different priorities. The majority class considers pulmonary symptoms to be as equally important of a therapeutic target as cardiac symptoms, whereas the minority cluster considers is to be less important. This may be due to lack of experience with a symptom or less advanced disease progression. Further research is needed to better understand heterogeneity for treatment target preferences and characteristics associates with those preferences.

4.7 References

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Chapter 5

Patient Preferences for Regulatory Review: Pulmonary Benefits in Duchenne Muscular Dystrophy

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5.1 Abstract

Background Incorporating patient preferences into regulatory decision-making in a scientific manner is particularly important for rare diseases with high degrees of uncertainty and in which reviewers have limited clinical experience. In direct response to guidance, a stated-preference study was conducted to measure patient preferences information for regulatory review of a therapeutic agent for Duchenne muscular dystrophy (DMD) that demonstrated pulmonary benefits in a phase III clinical trial. This paper quantifies patient and caregiver preferences for a therapeutic agent for DMD, a progressive neuromuscular disorder with expected pulmonary decline. We also explored differences in caregiver and patient preferences.

Methods A best-worst scaling case 2 survey with nine profiles was administered to 133 caregivers and patients with DBMD. Respondents selected the best and worst attributes from among 4 attributes at 3 levels. Utility scores were estimated using mixed logistic regression.

Results Respondents demonstrated greatest preference for therapies that maintain their current level of cough strength for 10 years ($score = 3.893; SE = 0.09$) or for 2 years ($score = 3.027; SE = 0.09$). Preference scores for risks were low; 50% chance of diarrhea ($score = -1.943; SE = 0.08$) and 4 additional blood draws per year ($score = -1.883; SE = 0.08$).

Conclusion Results demonstrate a strong preference for pulmonary benefit and willingness to trade-off risks and burden to achieve these benefits. In exchange for maintaining cough strength for 10 years, respondents were willing to tolerate high probabilities of diarrhea and additional blood draws. Although not powered to detect statistically significant differences, there were no qualitative differences in preferences between caregivers and patients.

5.2 Background

Regulatory decision-makers often lack reliable information to make data-driven patient-centered benefit-risk assessments. In an effort to rectify this, Congress mandated regulatory decision-makers incorporate patient preference information into benefit-risk assessment [1-2]. Patient-centered benefit-risk (PCBR) assessment is an increasingly-favored approach of doing this in a vigorous way [3]. Historically, the Food and Drug Administration (FDA) has relied on patient testimony for patient preference information. Although powerful, these anecdotes are biased, limited in their representation of diverse viewpoints, and fail to provide quantitative data about minimal benefit and acceptable risks.

The FDA has become increasingly interested in PCBR because of its ability to provide information about factors that patients and families will tradeoff in making decisions to use new technologies, including quantifying risk tolerance and minimum required benefit. The FDA has encouraged its reviewers to consider patients' perspectives when such information is available, and has participated in its own patient-preference study [4-5]. FDA staff have published editorials in scientific journals and the agency published guidance for drug developers, or sponsors, regarding what, how and when patient preference data may be considered during the review process [6-7]. As part of a public/private partnership, they have also been part of a consortium that developed a framework for incorporating patient preference information into regulatory assessments of new technologies [8]. The FDA has also highlighted the importance of this data for preference-sensitive decisions in which there is significant uncertainty and/or patients' views may differ considerably from those of researchers and clinicians [8].

Rare diseases provide a preference-sensitive context that is particularly well suited for incorporating patient preference information due to high unmet need, shortened lifespan, limited treatment options, and high degrees of uncertainty [7-8]. Furthermore, reviewers may have limited clinical or personal experience with a rare condition, increasing the likelihood that patient preferences differ from those of reviewers and clinicians [7-8].

Recognizing the relevancy for its patient population, Parent Project Muscular Dystrophy, an advocacy organization focused on finding a cure for Duchenne

muscular dystrophy (DMD), developed draft guidance for industry that calls for incorporating patient preferences [9-10]. The FDA followed with its own draft guidance for industry developing drugs for DMD that acknowledges patient and caregiver benefit-risk tolerance and preference heterogeneity should be considered in regulatory decisions [11]. DMD is a serious neuromuscular disorder of pediatric onset. It causes progressive muscle weakness with respiratory failure as the leading cause of death [12-16].

Despite significant progress in developing a framework and proposing processes for incorporating patient preferences in regulatory decision-making, it is still a nascent field with few examples of formal consideration of patient preference information in benefit-risk assessment for new drug therapies. As such, there is little understanding for how drug developers, or sponsors, will respond to the recent guidance and increasing emphasis on patient preferences.

Patient preference studies have been previously used to quantify patient preferences for hypothetical therapeutic options that would slow the progression of muscle weakness [17]. To our knowledge, the following paper is the first preference study to be developed in direct response to guidance for sponsors. The objective of this paper is to quantify patient and caregiver preferences for a therapeutic agent for DMD that demonstrated pulmonary benefits in a phase III clinical trial. The decline of pulmonary function is progressive and results in considerable morbidity and mortality typically following the loss of ambulation in the 2nd decade [12-16]. We hypothesize that caregivers and patients will be willing to trade moderate risk for pulmonary benefits. A secondary objective is to explore caregiver and patient preferences. We expect that caregivers and patients may have different preferences.

5.3 Methods

Survey development

A community-engaged approach was used to elicit feedback from key stakeholders regarding attribute selection and refinement. A total of 20 stakeholders were involved in over 15 hours of formal engagement over 4 months. The group was organized across three committees (leadership, stakeholder and review committee)

and provided feedback at various time points to allow for an iterative design approach. Additional details about the community-engaged approach and the model for survey development are published elsewhere (see Chapter 3).

The final survey included a best-worst scaling (BWS) case 2 (profile case) experiment with four attributes with three levels each, one of which was a reference level of no benefit or no risk. Benefits did not represent disease reversal, but rather were operationalized to offer a slowing of disease progression. The benefits included maintaining level of cough strength (maintain for 10 years, maintain for 2 years, or no benefit) and reducing the frequency of lung infections (very few infections, half as many, or no reduction). Risks included a common side effect to many drug therapies operationalized as diarrhea (no risk, 20% risk, or 50% risk) and a burden-related measure of blood monitoring frequency while on the treatment (no additional blood draws, two additional blood draws per year, or four additional blood draws per year).

Survey design

The computer-based survey was programmed and administered in Qualtrics. The survey was self-administered and included demographic questions about the respondent and clinical questions about the affected individual such as ambulation status, type of muscular dystrophy and history of steroid use. The survey consisted of four stated-preference exercises, however only the results of the BWS case 2 (profile) experiment and a follow-up simple discrete choice task are reported here. BWS is stated-preference method that has been developed more recently and continues to grow in popularity among healthcare applications [18-27]. In BWS case 2, respondents evaluate one treatment profile at a time and provide two data points per profile (best and worst) [28]. Across 9 choice tasks, respondents selected the best and worst attributes from among 4 attributes at 3 varying levels. See Figure 5.1 for an example choice task. Respondents could not advance to the next task without selecting both a best and worst choice, thereby forcing a choice.

After each treatment profile, respondents were asked about their intention to use this treatment if it were available to them. Concordant use of BWS case 2 and a simple conjoint analysis experiment in a single survey has been shown

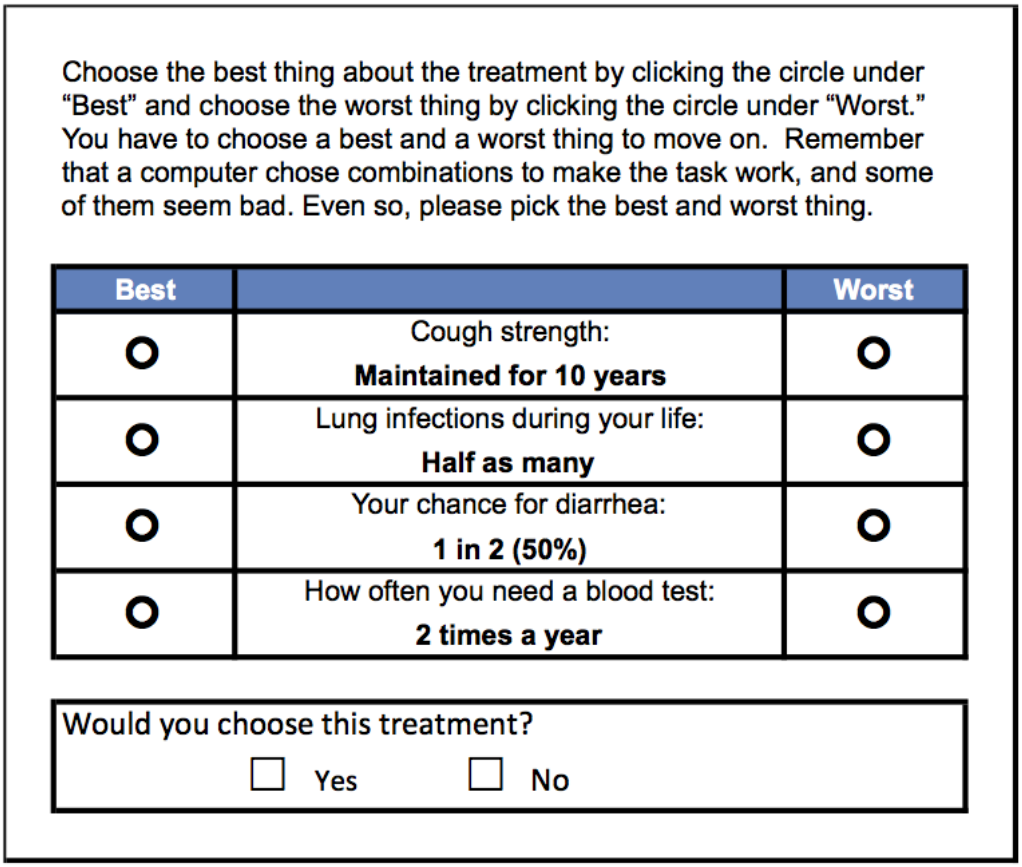

Figure 5.1: Sample choice task for BWS case 2 (profile) experiment and follow-up intention to use question.

to be useful for patient preference research intended to inform regulatory decisions making because the interpretation and application of the combination of data helps to understand risk tolerance, meaningful benefits, and explore intention to use specific therapies [29].

A 3^4 main effects orthogonal, fractional experimental design was used such that the attribute levels presented for each attribute across tasks were balanced and uncorrelated. This design is accessible and focuses on statistical efficiency because the minimum number of treatment profiles are used to ensure uncorrelated attributes [26,30-31]. The design was identified from the SAS database of orthogonal arrays [32].

Recruitment

Respondents were recruited through multiple sources targeted at qualifying respondents between June 18, 2015 and July 30, 2015. Recruitment initiated at the PPMD annual conference and was followed by targeted emails directed to DuchenneConnect registry participants. Respondents were also recruited through a grass-roots parent led outreach initiative of Parent Project Muscular Dystrophy (PPMD).

Eligibility criteria included living in the United States and being either the caregiver of someone living with Duchenne or Becker muscular dystrophy or a patient with the same condition. Caregivers had to be at least 18 years of age and their affected child was required to be at least 10 years old. The minimum age for patient respondents was 14 years. The protocol for this study was approved by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (IRB # 00006299). All participants provided informed consent electronically. Teen participants participated with a guardian's permission.

Analysis

Fischer's exact tests were used to test for differences in relevant characteristics of the affected individual with DBMD across caregiver and patient respondents. Differences for characteristics of the survey respondents were not tested because the groups are expected to be different.

The analysis assumes that the choice of the best and worst item represents the

extreme ends of a latent ranking of item importance and therefore the utility scores can be compared to represent the difference between the degree of importance among items [33]. Utility scores were estimated using mixed logistic regression with effects coding for the stratified samples (caregivers and patients) and the pooled sample. The forced choice design allowed for a complete case analysis. For the stratified analysis, caregiver and patient utility scores were compared using t-tests at the 95% confidence levels and with Bonferroni adjustments for multiple comparisons. Coefficients for the standard deviations of each attribute's choice are used to represent the degree of heterogeneity in an attribute. Using the aggregate analysis of combined caregivers and patients, coefficients for the means for the attribute/level combinations were rescaled such that the category representing no change from baseline is anchored at zero. Probabilities of intentions to treat were estimated by calculating the means for the respondents selecting that they would use the treatment. We calculated relative attribute importance using best-minus-worst scores by summing the number of times that an attribute was chosen as best or worst, regardless of the level. We conducted exploratory analyses looking at results stratified by respondent type (caregivers or patients). All analyses were conducted using STATA 14 (StataCorp LP, College Station, Texas).

5.4 Results

Descriptive statistics

A total of 133 respondents completed the BWS case 2 experiment comprised of 61.7% caregivers ($n = 82$) and 38.3% patients with DBMD ($n = 51$). Table 5.1 provides a complete list of respondent characteristics. Caregiver respondents were primarily biological mothers ($77\%, n = 63$). Other caregiver types included biological fathers ($16\%, n = 13$), adoptive mothers ($6\%, n = 5$) and grandmother acting as a guardian ($1\%, n = 1$). The majority of caregivers were married or in long-term relationships ($72\%, n = 59$). The mean age of participants was 46.8 years (SD=8) for caregivers and 27.7 years (SD=14) for patients. The majority of respondents were white ($88\%, n = 72$) and living in higher income households with 86.5% ($n = 71$) of caregivers and 47.2% ($n = 25$) living in households earning more than $50,000

per year.

	Caregivers (n=82)		Patients (n=51)	
	Frequency	Percent	Frequency	Percent
Survey respondents				
Respondent age				
14-18 years	0	0%	13	25%
18-30 years	0	0%	24	47%
30-45 years	36	44%	6	12%
45+ years	46	56%	8	16%
Respondent Race				
White	72	88%	47	92%
Hispanic	6	7%	4	8%
Native	4	5%	1	2%
Black	4	5%	2	4%
Asian	1	1%	2	4%
Other	1	1%	1	2%
Respondent household income				
<$50,000	13	16%	17	33%
$50,001 - $75,000	18	22%	8	16%
$75,001 - $100,000	24	29%	7	14%
>$100,000	16	20%	10	20%
Region				
Northeast	15	18%	10	20%
Midwest	15	18%	8	16%
South	29	35%	21	41%
West	23	28%	12	24%
Marital status				
Single	6	7%	29	57%
Married/long-term relationship	59	72%	9	18%
Divorced/separated/widowed	16	20%	0	0%
Caregiver respondents				
Relationship to affected individual				
Biological mother	63	77%	--	--
Biological father	13	16%	--	--
Adoptive mother	5	6%	--	--
Grandmother guardian	1	1%	--	--
Caregiver highest level of education			--	--
High school graduate	34	41%	--	--
College graduate	29	35%	--	--
Graduate/professional degree	18	22%	--	--

Note: Rows within a category may sum to less than 100% due to missing data. Race categories are not mutually exclusive. Blank fields are due to questions not asked of respondent category.

Table 5.1: Demographic characteristics of survey respondents.

As shown in Table 5.2, most affected individuals had a diagnosis of Duchenne muscular dystrophy. Although this was lower among adult respondents ($82\%, n = 42$) compared to caregiver respondents ($88\%, n = 72$), this was not a statistically significant difference. The majority of affected individuals had current or past his-

tory of steroid use. Caregivers reported that 83% ($n = 68$) of their affected children had current or past history of steroid use and 69% ($n = 35$) of patients reported current or past history of steroid use. The majority of affected individuals were either privately insured ($caregivers : 46\%, n = 38; patients : 39\%, n = 20$) or privately insured and received public insurance ($caregivers : 34\%, n = 28; patients : 45\%, n = 23$). Only mean age of the affected individual had a statistically significant difference between the caregiver group ($mean = 16.0, SD = 6$) and the patient group ($mean = 27, SD = 14$). This is expected given the eligibility criteria for participation. There was also a wider range for the age of the patient group, which is consistent with the larger proportion of respondents in that group with Becker muscular dystrophy, which is associated with longer lifespan.

	Caregivers (n=82)		Patients (n=51)		
	Frequency	Percent	Frequency	Percent	
Individuals affected with DBMD					
Age					§
10-13 years	36	44%	n/a	n/a	
14-17 years	26	32%	13	25%	
18-25 years	14	17%	16	31%	
25+ years	6	7%	22	43%	
Diagnosis					
Duchenne	72	88%	42	82%	
Becker	8	10%	9	18%	
Intermediate	2	2%	0	0%	
Ambulation status					
Ambulatory	34	41%	14	27%	
Non-ambulatory	48	59%	37	73%	
Steroid use					
Current or previously	68	83%	35	69%	
Never	13	16%	16	31%	
Insurance type					
Private	38	46%	20	39%	
Public	16	20%	8	16%	
Both	28	34%	23	45%	

§ = statistically significant difference at the p<0.01 level; n/a = not applicable.
Note: Rows within a category may sum to less than 100% due to missing data.

Table 5.2: Demographic and clinical characteristics of affected individuals.

Utility scores

The results of mixed logit analyses for the stratified groups are shown in Table 5.3. Respondents demonstrated the greatest preference for a therapeutic agent that maintains their current level of cough strength for 10 years ($caregivers: score = 1.697, 95\%CI = [1.44, 1.95]; patients: score = 1.446, 95\%CI = [1.19, 1.74]$) and for 2 years ($caregivers: score = 0.716, 95\%CI = [0.49, 0.94]; patients: score = 0.746, 95\%CI = [0.44, 1.05]$). Though respondents preferred half as many lung infections ($caregivers: score = 1.118, 95\%CI = [0.90, 1.34]; patients: score = 0.907, 95\%CI = [0.65, 1.16]$) over very few lung infections ($caregivers: score = 0.790, 95\%CI = [0.52, 1.06]; patients: score = 0.870, 95\%CI = [0.59, 1.15]$),the overlap in the confidence intervals between the two levels demonstrate no significant difference in preferences.

Attribute/level	Caregivers		Patients		Difference test
	Coef. (SD)	(95% CI)	Coef. (SD)	(95% CI)	P-value
Cough strength maintained for 10 yrs	1.697 (0.49)	(1.44 , 1.95)	1.466 (0.03)	(1.19 , 1.74)	0.23
Cough strength maintained for 2 yrs	0.716 (0.32)	(0.49 , 0.94)	0.746 (0.48)	(0.44 , 1.05)	0.88
Cough strength maintained at current rate	-2.413 (0.30)	-(2.70 , -2.13)	-2.212 (0.35)	-(2.54 , -1.88)	0.37
Very few lung infections	0.790 (0.79)	(0.52 , 1.06)	0.870 (0.38)	(0.59 , 1.15)	0.68
Half as many lung infections	1.118 (0.35)	(0.90 , 1.34)	0.907 (0.16)	(0.65 , 1.16)	0.22
No reduction in lung infections	-1.908 (0.25)	-(2.21 , -1.61)	-1.777 (0.41)	-(2.08 , -1.47)	0.55
0% risk of diarrhea	1.311 (0.02)	(1.11 , 1.51)	1.009 (0.11)	(0.77 , 1.25)	0.06
20% risk of diarrhea	-0.428 (0.02)	-(0.63 , -0.23)	-0.448 (0.01)	-(0.70 , -0.20)	0.90
50% risk of diarrhea	-0.884 (0.24)	-(1.08 , -0.68)	-0.561 (0.34)	-(0.81 , -0.31)	0.05
No additional blood draws per year	1.113 (0.01)	(0.91 , 1.32)	0.973 (0.02)	(0.73 , 1.22)	0.39
2 additional blood draws per year	-0.308 (0.01)	-(0.51 , -0.11)	-0.109 (0.03)	-(0.35 , 0.13)	0.22
4 additional blood draws per year	-0.805 (0.27)	-(1.01 , -0.60)	-0.864 (0.37)	-(1.12 , -0.61)	0.72

Note: Coef = coefficient (mean) from mixed logistic regression; 95% CI = 95% confidence interval around the coefficient; SD = standard deviation of the mean; P-value represents the result of the difference in means test between two groups.

Table 5.3: Mixed logit results for caregiver and patients preferences for benefits and risks.

Respondents had the lowest preference for a therapeutic agent with no benefit to cough strength ($caregivers: score = -2.413, 95\%CI = [-2.70, -2.13]; patients: score = -2.212, 95\%CI = [-2.54, -1.88]$) followed by an agent with no benefit to

lung infections ($caregivers: score = -1.908, 95\%CI = [-2.21, -1.61]; patients: score = -1.777, 95\%CI = [-2.08, -1.47]$)-these were preferred less than even a 50% risk of diarrhea ($caregivers: score = -0.884, 95\%CI = [-1.08, -0.68]; patients: score = -0.561, 95\%CI = [-0.81, -0.31]$).

As shown in Table 5.3, the differences in preference scores were not statistically significantly different across caregiver and patient groups. Furthermore, the standard deviations of the preference scores are not statistically significant for 75% of the attribute/level combinations (see Table 5.3). A $p - value < 0.05$ indicates statistically significant heterogeneity. However, results indicate statistically significant heterogeneity only for cough strength maintained for 10 years, very few lung infections, and no reduction in lung infections among caregivers and only for cough strength maintained for 2 years among patients. Overall, comparing caregiver and patient preferences for DBMD treatments showed no significant quantitative differences and no qualitative differences between the two groups. Therefore, to understand attribute importance, minimal acceptable benefit and maximum acceptable risk, pooled results are shown. See Figure 5.2.

Relative attribute importance revealed that respondents were most concerned with a treatment's ability to address benefits compared to a treatment's risks. Results were similar across both groups and there were no statistically significant differences between them. Cough strength had the greatest importance (38.3%), followed by fewer lung infection (26.5%), diarrhea (18.6%) and blood draws (16.5%).

Intention to use treatments

As shown in Figure 5.3, for 8 of 9 profiles there was a more than 65% probability that respondents intend to use the treatment. For four treatment profiles, there was a probability greater than 80% of use. All of these profiles had a benefit of maintaining cough strength for at least two years and three of four had a moderate benefit for lung infections. For most treatment profiles there were no significant differences between caregivers and patients, with one exception. Treatment profile E had a 57% probability of take-up among patients and a 76% probability of take-up among caregivers.

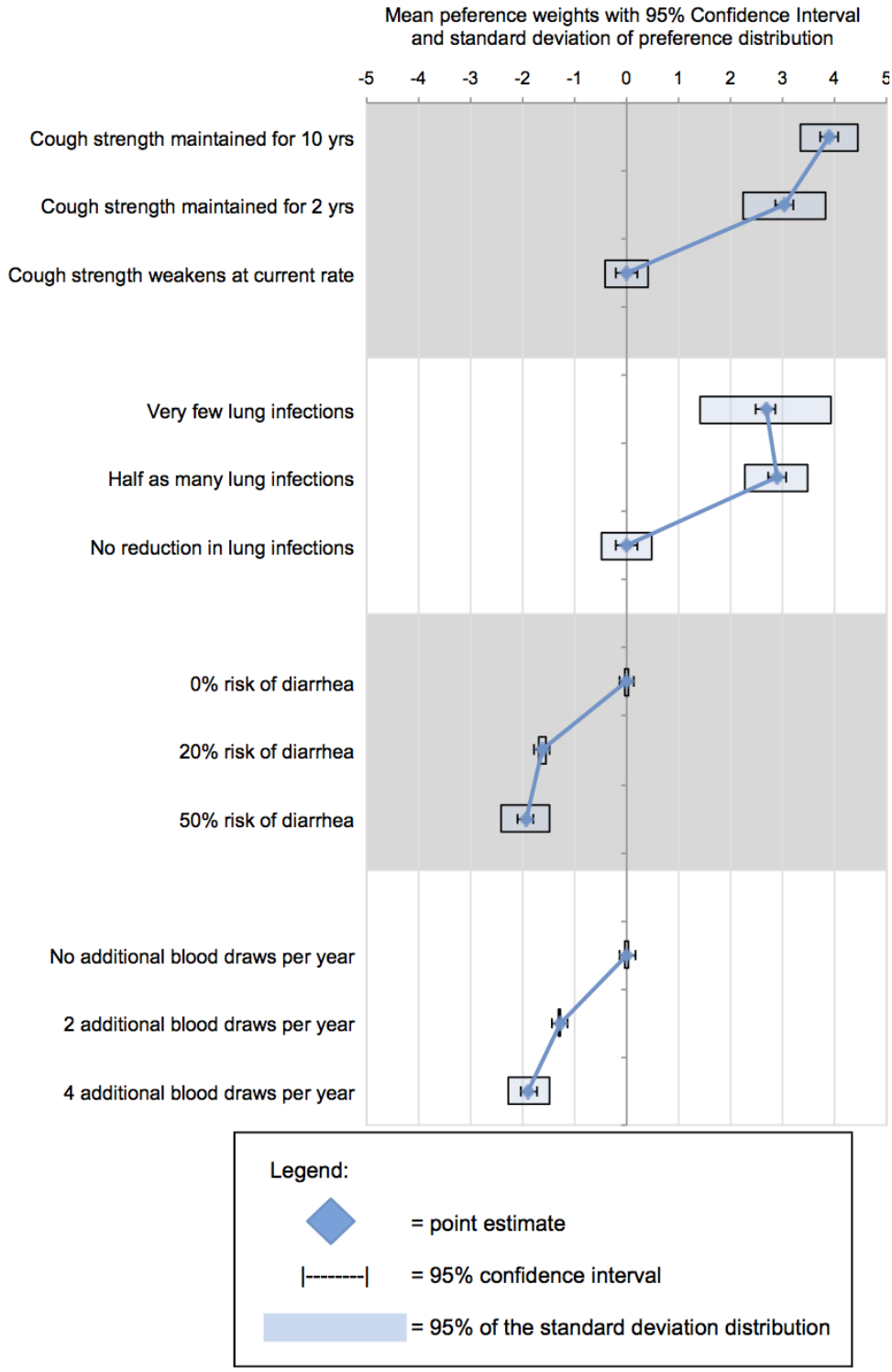

Figure 5.2: Mixed logit results for aggregate preferences for benefits and risks.

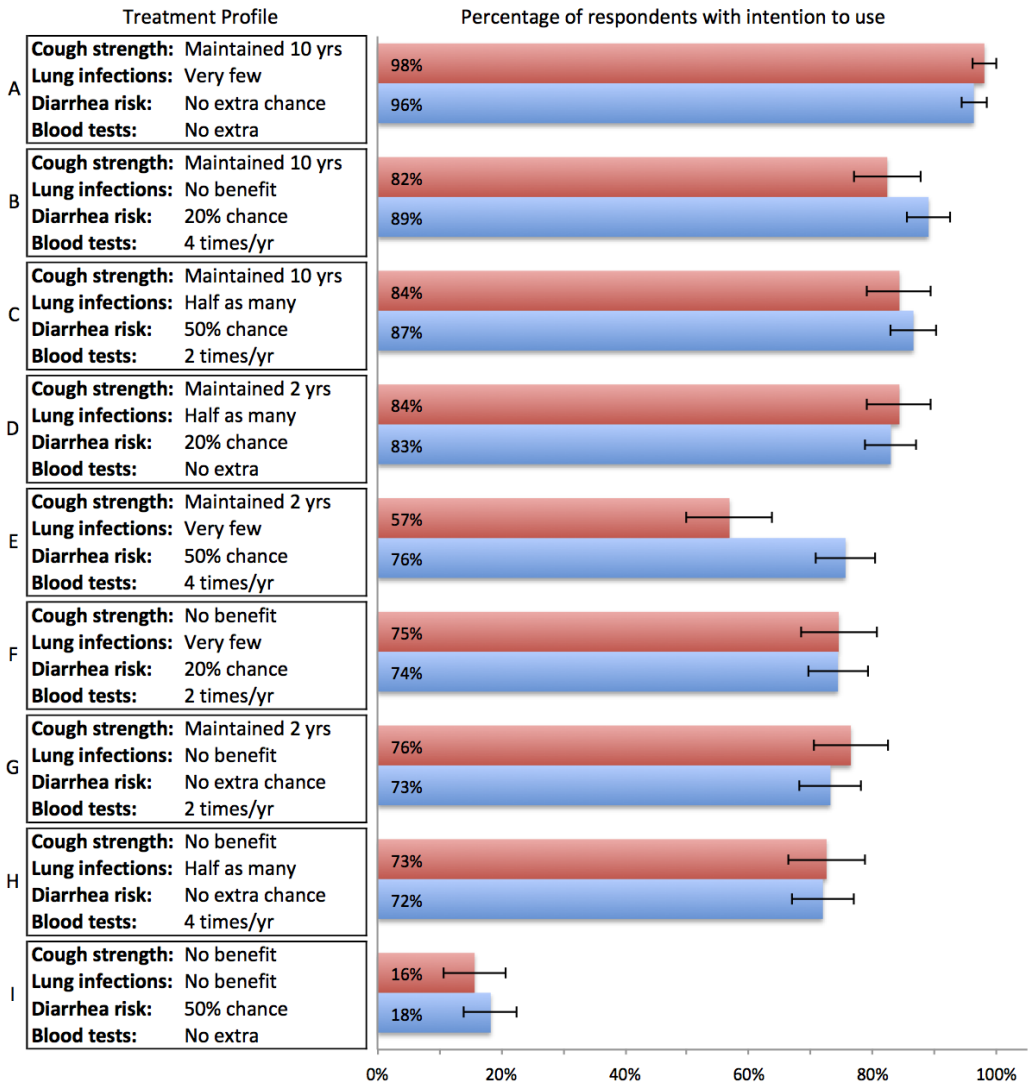

Figure 5.3: Probability representing intention to use treatment profile by respondent type and corresponding treatment profiles.

5.5 Discussion

Overall, caregivers and patients endorsed similar preferences for DBMD treatments. Respondents demonstrated greatest preference for maintaining cough strength and reducing the number of lung infections compared to the risk of diarrhea and additional blood monitoring. The maximum risk that participants were willing to accept was a 50% increased risk for diarrhea in addition to the burden of twice yearly blood monitoring, in order to maintain their current level of cough strength for up to 10 additional years. The maximum risk that participants were willing to accept in order to maintain their cough strength for two years was 20% risk of diarrhea and blood monitoring an additional two times per year.

Preference scores for "no benefit to cough strength" and "no benefit to lung function" are the lowest, which demonstrates that respondents prefer some risk over no benefit to cough strength or lung infections. This has important implications for quantifying the patient and caregiver's willingness to trade-off-information that should be used to inform regulatory decision-makers for benefit-risk assessments.

These findings were supported by data resulting from the follow-up discrete choice question, in which participants were asked about whether they intend to use the treatment. A large majority of respondents were willing to try a treatment that offers a moderate benefit even with the highest levels of risk and burden (see profile E in Figure 5.3). This information is also important for regulators in terms of understanding whether people are likely to use a therapy if approved.

For BWS experiments it is important that the attributes are independent of one another. This is both for the statistical design properties and because respondents may be confused by overlapping attributes if a profile seems to have contradictory attribute levels. Although cough strength and lung infections are both related to pulmonary function, the data exhibit no signs of serial non-attendance to any one attribute, which indicates respondents differentiated between the two pulmonary measures. Furthermore, there were no signs of universal acceptance indicating that participants were actively making trade-offs.

Unexpectedly, the results for the lung infection attribute were not monotonic. "Very few lung infections" was the level designed to represent the greatest improvement in frequency of lung infection; however, respondents chose it as worst more

often than they chose “about half as many lung infections” as worst, which was designed to be the middle level of benefit. Respondents had an educational portion prior to the choice tasks in which they were provided with assumptions about the attribute and level definitions, because ”very few” is not quantifiable whereas ”half as many” is quantifiable, the ordinal nature of the levels may not have been obvious within a single profile. Thus, respondents may have misinterpreted “very few” to mean an amount less than ”half as many.” This misinterpretation was not detectable through cognitive interviewing and pre-testing, but became discernible once responses were analyzed in aggregate. Regardless of the lack of monotonicity, the lung infection attribute was perceived as an important benefit.

Overall, greater importance reported towards the benefits relative to the risks demonstrates favorable benefit-risk profile, such that people are likely to accept the risks of diarrhea and blood monitoring in exchange for the benefit of maintaining cough strength and decreased lung infection. This finding should be considered with an understanding that the attributes and levels represented in this study do not directly reflect the phase III clinical trial outcomes. Similarly, the inclusion criteria for the survey do not mirror the inclusion criteria for clinical trial participants. This was not a limitation, but rather a strategy undertaken so that the stated-preference survey results would inform regulators about meaningful benefits-risk tradeoffs in a broader population.

5.6 Conclusion

The results demonstrate a strong preference for therapies with a pulmonary benefit and willingness to trade-off risks and burden to achieve these benefits. Specifically, in exchange for maintaining cough strength for 10 years, respondents are willing to tolerate high probabilities of diarrhea and the burden of additional blood draws.

Incorporating patient preferences into benefit-risk assessment at the regulatory level is important for patient-centered drug development. The implications are highly relevant in a rare disease context like DBMD because many decisions are preference-sensitive, in part due to the high degree of uncertainty with regards to the treatment outcomes. Furthermore, patient preference information can highlight potential differences in views between clinicians and patients, something that is

also more likely among rare diseases because reviewers likely have limited clinical exposure to the disease.

The future of patient-centered drug development is in the power of quantifiable, scientific preference data to complement efficacy data. This study demonstrates the capacity of community-engaged preference research to provide data about variables that are meaningful to patients and families. Furthermore, it demonstrates the influence of FDA guidance in promoting the use of such methods to inform the drug development process.

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Chapter 6

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

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[2] A version of this manuscript was published in *The Patient* in February 2015.

6.1 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. Our objective was to compare two stated-preference methods, best-worst scaling (BWS) and con-joint 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.

6.2 Background

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.

6.3 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.

Experimental Design

Using a community-engaged approach, the research team identified six relevant treatment attributes, or categories of characteristics (shown in Table 6.2), each

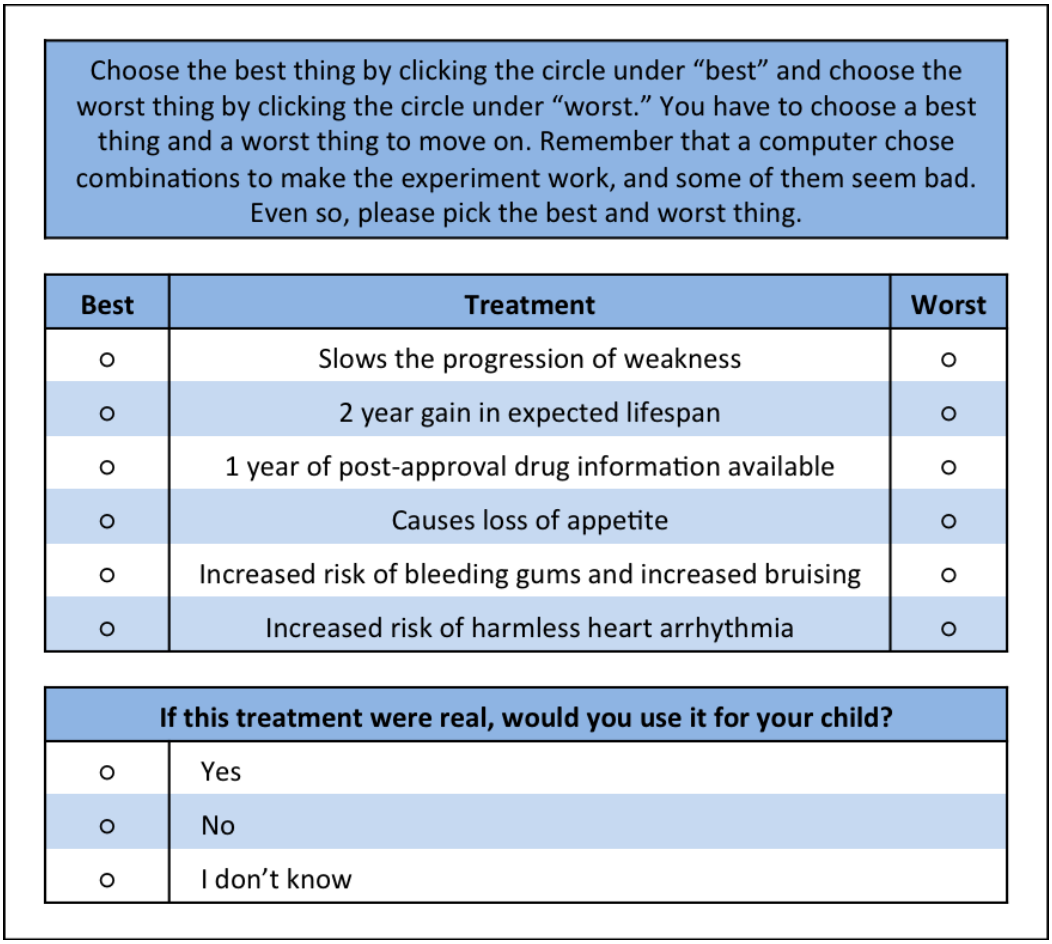
with three levels. The levels indicate varying degrees of change to represent no increased risk, mild to moderate risks, or severe risks; and no change, modest change, and moderate change in benefit [19]. The development of the attributes and levels was informed by multiple stakeholders, an oversight 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 "don't know." Figure 6.1 illustrates an example of the paired BWS and conjoint analysis task from the survey instrument.

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.



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

Figure 6.1: Survey instrument example task: combined best-worst scaling and conjoint 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 "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 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.

6.4 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 $US 100,000 per year. More than 90 % reported that their child had participated in clinical research or a clinical trial. See Table 6.1 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 6.2), we present BWS results using conditional 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 6.2 presents a graphical representation comparing preference weights across the two methods.

Table 6.3 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 6.3). The conditional attribute importance was concordant across BWS and conjoint analysis ($Spearman's \rho = 0.943; p < 0.01$).

Finally, the concordance between BWS and conjoint analysis was again con-

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

Table 6.1: Characteristics of participants and affected child(ren) (n = 119).

	Best-Worst Scaling		Conjoint Analysis	
Variable	Coef.	Std. Err.	Coef.	Std. Err.
Effect on muscle function				
Stops the progression of weakness	1.447	0.066	0.860	0.084
Slows the progression of weakness	1.161	0.080	0.353	0.067
Does not change the progression of weakness	-2.608	0.134	-1.213	0.116
Lifespan				
5 year gain in expected lifespan	0.942	0.058	0.581	0.069
2 year gain in expected lifespan	0.717	0.060	0.118	0.056
No extra gain in expected lifespan	-1.658	0.094	-0.698	0.084
Knowledge about the drug				
2 years of post-approval drug info available	0.301	0.052	-0.187	0.076
1 year of post-approval drug info available	0.066	0.039	0.168	0.049
No post-approval drug info available	-0.366	0.069	0.019	0.076
Nausea				
No increased change of nausea	0.707	0.055	-0.185	0.066
Causes loss of appetite	0.070	0.046	0.164	0.056
Causes loss of appetite with occasional vomiting	-0.777	0.062	0.021	0.078
Risk of bleed				
No increased risk of bleeds	1.429	0.058	0.772	0.081
Increased risk of bleeding gums and increased bruising	0.302	0.062	0.268	0.067
Increased risk of hemorrhagic stroke and lifelong disability	-1.731	0.081	-1.039	0.108
Risk of heart arrhythmia				
No increased risk of heart arrhythmia	1.280	0.060	0.716	0.081
Increased risk of harmless heart arrhythmia	0.724	0.068	0.417	0.065
Increased risk of dangerous arrhythmia and sudden death	-2.004	0.090	-1.133	0.114

Table 6.2: Comparison of parameter estimates based on best-worst scaling and conjoint analysis results.

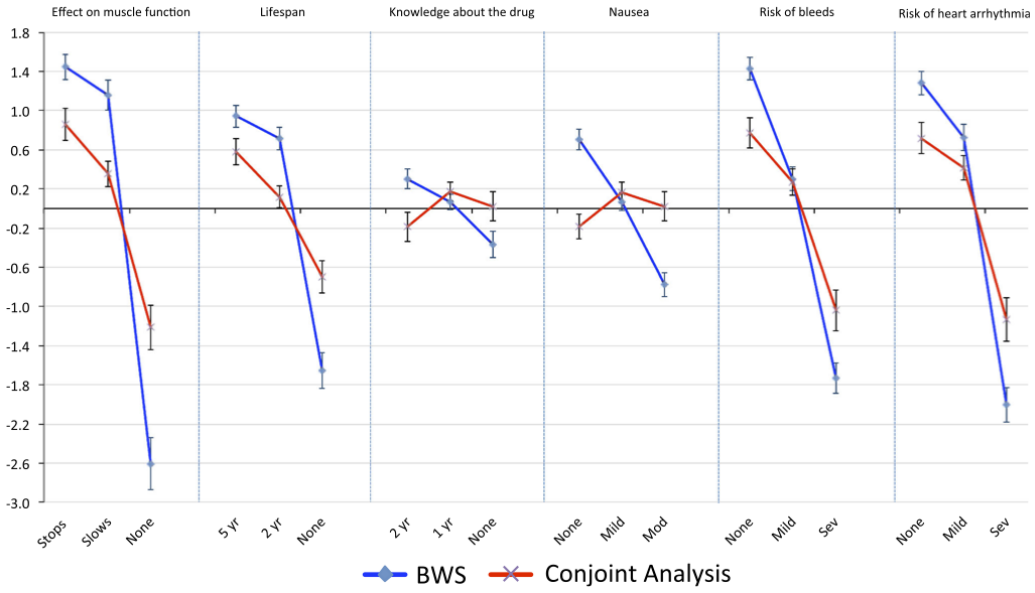


Figure 6.2: Comparison of best-worst scaling and conjoint analysis results.

	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

Table 6.3: Comparison of conditional attribute importance.

firmed through comparative policy analysis, and rank ordering was concordant ($p < 0.01$). As seen in Table 6.4, 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.

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

Table 6.4: Comparative policy analysis.

6.5 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 6.3), and net utility of treatment profiles compared with probabilities of accepting the treatment (see Table 6.4). 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 6.3). We conducted two post hoc analyses (stratified analysis based on disease severity and two-group latent 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 eval-

uate 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 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 6.4, 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.

6.6 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.

6.7 References

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Chapter 7

Conclusions

7.1 Summary of findings

The first key finding of this work is the demonstration of a successful process for engaging the community in survey development. The engagement process was critical for identifying appropriate eligibility criteria, refining attributes for the survey and revealing the delicate nature of mapping clinical trial endpoints to meaningful survey objects (Chapter 3). The second key finding of this dissertation is that caregivers and patients did not differ in their priorities for signs and symptoms to be targeted by therapeutic interventions. Both groups favored targeted cardiac and pulmonary symptoms such as weaker heart pumping, cough strength and frequency of lung infections. The lowest priority symptom was poor attention span. Chapter 4 findings indicate the existence of heterogeneity among priorities, although the differences may be related to unobserved characteristics. In Chapter 5, findings reveal patients were willing to accept significant risk for moderate improvements in pulmonary decline. Specifically, in exchange for maintaining cough strength for 10 years, respondents were willing to tolerate high probabilities of diarrhea and additional blood draws. Although not powered to detect statistically significant differences, there were no qualitative differences in preferences between caregivers and patients. Again, heterogeneity was present for these preferences. Finally, methodological findings in Chapter 6 indicate that a follow-up question in best-worst scaling surveys about intention to use a particular therapy adds useful, policy-relevant information. It also serves to validate the best-worst-scaling case 2

method.

7.2 Policy implications

There are implications for this dissertation that are specific to Duchenne muscular dystrophy as well as the broader rare disease community. First, for the Duchenne muscular dystrophy community this dissertation measures patient priorities, which contributes to the overall body of knowledge around patient preferences in Duchenne muscular dystrophy and as a result improves the usefulness of future development. It also quantifies patient preferences for a pulmonary benefit, information that will be incorporated into regulatory review and may contribute to an outcome that meets the community's needs. Second, the implications for the broader rare disease community are that a model exists for how rare diseases can undergo this research. It also brings to light the ways that preference information can be incorporated into other policy research areas relevant to rare diseases such as advancing research and ensuring access to treatments. This research also underscores the importance of preference work in the rare disease community specifically because of its unique needs.

Furthermore, this dissertation advances the body of research related to stated-preferences more generally. This research provides a model for how industry and/or advocacy organizations can conduct stated preference studies to contribute to patient-focused drug development. In Chapter 3, I demonstrate a process for how industry, advocacy, and methodological experts can collaborate with the patient community to design a patient-centered survey. In Chapter 4, I demonstrate how patient preference information can be collected to inform early stages of drug development such as needs assessment and can contribute to a body of knowledge on patient preferences. In Chapter 5, I demonstrate how patient preferences can be quantified to directly inform patient-centered benefit-risk assessment. In Chapter 6, I demonstrate that these methods are feasible and accessible, and that they produce the right information required to inform regulatory review. This dissertation as a whole paves the way for future innovators to study, and incorporate patient preferences into drug development work.

Providing this information to the FDA and continuing to emphasize the im-

portance of patient preferences in the decision-making process may exert pressure on the FDA to consider preference data as an important part of regulatory review. In an ideal case, the FDA will formally incorporate preference information into the benefit-risk framework, requiring it as part of their regulatory review process for preference sensitive conditions. This could have tremendous potential spillover effects due to the global economic and scientific reach of the FDA's power [1]. The FDA's power, derived from its regulation of the entry into the US pharmaceutical marketplace, positions the FDA to play a pivotal role in advancing patient-centeredness and have widespread influence in patient-centered drug development around the world.

Patient preference methods require expertise and are expensive and time consuming. Therefore these methods may need to be reserved for situations with the greatest degree of uncertainty, complexity or contention [2]. Furthermore, these methods aren't easily scalable or generalizable. However, there is a role for patient preferences in each phase of the drug development life cycle and patient-focused drug development has the potential to impact a variety of stakeholder [3].

We demonstrated how preference information can contribute to the discovery and ideation phase (Chapter 4) and to the regulatory review phase (Chapter 5). There is room for future work around preference information in the clinical trial phase, specifically related to end-point selection. Preference information in benefit-risk assessment in the post-marketing phase will be an important part of future work as well. As we learn about the drugs from post-market surveillance, benefit-risk information must be updated [4]. The context surrounding benefits and risks may change as well. For instance a drug may go from being the only available option to one of many. Another important aspect of post-market research may be related to comparative effectiveness research and how individual patient preferences may be used to aid in their decision-making at the clinical encounter level. Future research opportunities include shared-decision making tools that incorporate patient preference information into a personal benefit-risk assessment.

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Appendix: Benefit-risk survey (Adult patient version)

ADULT PATIENT VERSION OF BENEFIT-RISK SURVEY

This survey is an experiment to learn about your priorities and preferences about treatments for Duchenne and Becker muscular dystrophy (DBMD). This survey is for adults with DBMD who are over 18 years old. There is another version of the survey for your parent and a version of the survey for adults with DBMD to answer. Click here if you are not a teen and want to see links to other versions of the survey.

In this survey you will read about treatments for DBMD. Some parts of the treatments used in this survey are real but other parts are made up. This information is important to help the FDA and others understand your thoughts and feelings about potential future DBMD treatments.

It is possible that these questions might make you feel upset because they deal with the effects of DBMD on the body. It is your choice to answer the survey. You can stop taking the survey at any time. The survey information is anonymous, meaning that no one knows who participates and what answers they give.

The survey takes about 1 hour. As long as you use the same computer, you can answer some of the questions and take a break (your answers will be saved) and go back to the survey later. There are no right or wrong answers; we ask you to share your honest opinions and feelings. If you have questions or concerns about this survey, please contact Holly Peay at holly@parentprojectmd.org.

Screening Questions

1. Are you 18 years of age or older? YES / NO

2. Do you have Duchenne or Becker muscular dystrophy? YES / NO

3. Do you live in the United States? YES / NO

   If answer to any of the above in No…
   Thank you for your interest, but you do not qualify for the study. If you would like to access the version of the survey for parents, please Click here. If you would like to access the version for teens with DBMD please Click here.
   Click here to exit survey.

4. Taking this survey is your choice. You can stop taking the survey at any time. If you agree to participate, please click the Yes button. If not, click the No button. YES / NO

   If No…
   Thank you for your consideration. Click here to exit survey.

Background Questions

First, please answer a few questions about yourself.

1. How old are you? [Pull down menu with younger than 18 disqualified]

2. What is your marital status? (Please choose the answer that best applies to your situation)

    a. Single
    b. Married or long-term committed relationship
    c. Divorced or separated
    d. Widowed

3. Are you Hispanic or Latino? YES / NO

4. Which of the following racial groups best describes you? (please select all that apply)

    a. American Indian or Alaskan Native
    b. Asian
    c. Black or African American
    d. Native Hawaiian or Other Pacific Islander
    e. Hispanic or Latino
    f. White
    g. Other: please specify _____

5. What is the highest level of education you have completed? (select only one answer)

    a. Less than some high school
    b. Some high school
    c. High school or GED
    d. Some college but no degree
    e. Technical School (currently enrolled or completed)
    f. Associate's Degree (2-year college degree)
    g. 4-year college degree (e.g., BA, BS)
    h. Some graduate school but no degree
    i. Graduate or professional degree (e.g., MBA, MS, MD, PhD)

6. What is your annual household income?

    a. Less than $24,000
    b. $24,000-$50,000
    c. $5,001-$75,000
    d. $75,001-$100,000
    e. More than $100,000
    f. Prefer not to answer

7. What state do you live in? [pull-down menu]

8. What is your diagnosis?

    a. Duchenne muscular dystrophy
    b. Becker muscular dystrophy
    c. Intermediate muscular dystrophy
    d. I don't know

9. Choose the option that best describes your physical abilities. Everyone is unique, and you may not match the descriptions perfectly. Please select the answer that is the best fit. I usually:

    a. Walk independently for long distances outdoors (more than 1⁄2 mile)
    b. Walk independently for less than 1⁄2 mile, but more than short distances
    c. Walk independently outdoors for short distances (such as to the car)
    d. Walk outdoors with help from a person
    e. Walk independently indoors but needs a wheelchair for outdoors
    f. Walk indoors with help from a person but need a wheelchair for outdoors
    g. Use wheelchair and can go indoors and outdoors
    h. Use wheelchair but unable to go outdoors in some situations (such as cold weather)
    i. Unable to control wheelchair without help
    j. Not using wheelchair. Remain in bed.

10. Have you ever used corticosteroids?

    a. Currently using prednisone/prednisolone
    b. Currently using deflazacort
    c. Used to take corticosteroids but not anymore
    d. Never used corticosteroids
    e. I do not know

11. What type of health insurance do you use for medical care? (select all that apply)

    a. Private Health Insurance
    b. State/government program, such as Medicaid/Medicare
    c. No insurance
    d. Other (please specify)
    _____

Section 1: Signs & Symptoms to be Treated

Think about new treatments for Duchenne and Becker muscular dystrophy (DBMD). The treatments would not be a cure but could help reduce the effects of DBMD. First, we will describe a number of signs and symptoms. Then we will ask you to give your opinion about what signs and symptoms are most important to you in developing new treatments.

These are signs and symptoms that often become more problematic as people with DBMD get older. Read the descriptions of the signs and symptoms below. First we will ask you to answer some questions about your experience with each symptom. Then, in the first task, you will answer more questions to see which symptoms are most important to you.

Here are the signs and symptoms that are used in the task.
[The online survey randomizes the order in which these are presented]

Weaker ability to cough: As DBMD progresses and with decline in respiratory function, the ability to cough forcefully may be lost. A strong cough is important for clearing the airway and letting the person get a good deep breath. Some people use devices (such as cough assist, BIPAP or CPAP) to help them cough or breathe better.

Have you ever used cough assist, BiPAP, CPAP, or had a tracheostomy?
YES / NO

Lung infections: Getting an infection in the lungs requires going to the doctor and taking antibiotics. Serious infections like pneumonia have to be treated in the hospital and might make it harder for the lungs to work well over time.

Have you ever been treated for pneumonia? YES / NO

Weaker heart pumping: Over time, people with DBMD's hearts can't squeeze as strongly as they used to. This means that they have to take heart medicines to help the heart pump.

Do you take any heart (cardiac) medication? YES / NO

Frequent waking at night: Teens and adults with DBMD may have more trouble sleeping soundly through the night, partly due to decline in lung function. People with this problem may need more help from caregivers to sleep comfortably.

In the past 7 days, I had trouble staying asleep…
Never / Rarely / Sometimes / Often / Always

Bone fractures: Bones can become weaker once a person with DBMD stops walking, and also from taking steroids. Weak bones lead to an increased chance of broken bones.

Have you had any broken bones (bone fractures)? YES / NO

Constipation: People with DBMD may have trouble with constipation (going more than 2 days without a bowel movement) due to immobility or medication side effects.

> In the past 7 days, how often did you have a bowel movement?
> 2 times or less / 3 to 6 times / Once a day / 2 to 3 times a day / More than 3 times a day

Headaches: Most people get headaches every once in a while. But frequent bad headaches can become more common in teens and adults with DBMD and may be caused by poor respiratory functioning.

> During the past 7 days, how many headaches have you had?
> 2 times or less / 3 to 6 times / Once a day / 2 to 3 times a day / More than 3 times a day

Feeling tired: After they wake up and throughout the day, people with DBMD may have more trouble with feeling tired than other people (also known as "daytime sleepiness").

> In the past 7 days how often have you felt tired?
> Never / Almost never / Sometimes / Often / Almost always

Non-healthy weight: People with DBMD can have trouble with gaining enough weight, while others have the problem of gaining too much weight.

> Which best describes your weight?
> Weigh too much / Healthy weight / Weigh too little

Poor attention span: Some people with DBMD experience more problems with paying attention and staying focused on a task than other people.

> Do you have difficulty concentrating and focusing during the day?
> Never/Almost Never / Sometimes / Often / Almost always

Depression: Living with DBMD may increase the chance for symptoms of depression, such as feeling sad, irritable, or not being interested in activities.

> In the past 7 days how often could you not help feeling sad?
> Never / Almost never / Sometimes / Often / Almost always

Task 1.

It's time for the first preference task. Keep in mind the descriptions of the symptoms that you just read. In each of the lists below, which of these symptoms are the most important for new treatments to improve? Which are the least important?

Your answers should be based on your own opinion and experiences. This is not a test. There are no right or wrong answers.

Here is an example:

Mike is taking the survey. He sees this table describing signs and symptoms of DBMD.

		Most important to treat	Least important to treat
A	Headaches	O	O
B	Depression	O	O
C	Feeling tired	X	O
D	Constipation	O	O
E	Poor attention span	O	X

Mike looks at the items in the list: headaches, depression, feeling tired, constipation, and poor attention span. He has to choose which symptom is the MOST important for a new treatment to improve and which is the LEAST important to improve. Based on his own experience and opinion, Mike thinks that "feeling tired" is the most important, so in the "Most important to treat" column he clicks the circle next to "feeling tired." He thinks that "poor attention span" is the least important to treat, so in the "Least important to treat" column he clicks the circle next to "poor attention span." Mike finds this difficult because he actually thinks that all of these are important, but he is able to make a choice.

[on each screen: Choose the most important symptom for a new treatment to improve by clicking the circle under "Most important to treat" and choose the least important symptom by clicking the circle under "Least important to treat." You have to choose a most important and a least important item to move on.]

1		Most important to treat	Least important to treat
A	Feeling tired	O	O
B	Depression	O	O
C	Weaker ability to cough	O	O
D	Bone fractures	O	O
E	Poor attention span	O	O

2		Most important to treat	Least important to treat
A	Headaches	O	O
B	Poor attention span	O	O
C	Depression	O	O
D	Frequent waking at night	O	O
E	Non-healthy weight	O	O

3		Most important to treat	Least important to treat
A	Frequent waking at night	O	O
B	Headaches	O	O
C	Feeling tired	O	O
D	Weaker ability to cough	O	O
E	Constipation	O	O

4		Most important to treat	Least important to treat
A	Weaker heart pumping	O	O
B	Constipation	O	O
C	Headaches	O	O
D	Depression	O	O
E	Bone fractures	O	O

5		Most important to treat	Least important to treat
A	Weaker ability to cough	O	O
B	Frequent waking at night	O	O
C	Bone fractures	O	O
D	Non-healthy weight	O	O
E	Weaker heart pumping	O	O

6		Most important to treat	Least important to treat
A	Lung infections	O	O
B	Bone fractures	O	O
C	Constipation	O	O
D	Poor attention span	O	O
E	Frequent waking at night	O	O

7		Most important to treat	Least important to treat
A	Bone fractures	O	O
B	Feeling tired	O	O
C	Non-healthy weight	O	O
D	Lung infections	O	O
E	Headaches	O	O

8		Most important to treat	Least important to treat
A	Constipation	O	O
B	Non-healthy weight	O	O
C	Poor attention span	O	O
D	Weaker heart pumping	O	O
E	Feeling tired	O	O

9		Most important to treat	Least important to treat
A	Non-healthy weight	O	O
B	Weaker ability to cough	O	O
C	Lung infections	O	O
D	Constipation	O	O
E	Depression	O	O

10		Most important to treat	Least important to treat
A	Depression	O	O
B	Weaker heart pumping	O	O
C	Frequent waking at night	O	O
D	Feeling tired	O	O
E	Lung infections	O	O

11		Most important to treat	Least important to treat
A	Poor attention span	O	O
B	Lung infections	O	O
C	Weaker heart pumping	O	O
D	Headaches	O	O
E	Weaker ability to cough	O	O

You are finished with the first task.

Section 2. Treatment Preferences

We now describe possible treatments that are based on some qualities of a real drug. Because of the way this type of research is run, some of the side effects and risks in this survey are more serious than we expect in real life. So you will be seeing made-up treatments with some realistic parts and some not so realistic parts.

Imagine that these are approved treatments given by your doctor, and not part of a clinical trial. The treatments have different benefits and risks. The average result can help you understand what you might expect for yourself.

We describe different possibilities for the treatment below. Please read carefully. Later in the survey we ask you questions about these treatment possibilities.

Cough Strength

Taking the medicine may help slow the impact of DBMD on the ability to cough. A weak cough is part of the progression of DBMD as people get older and their lung function gets worse. A strong cough is important for clearing the airway and letting you get a good deep breath. Here are the ways the medicine could help your ability to cough:

- **"Cough strength: maintained for up to 10 years**" This means that your cough would stay as strong as it is now for an average of **10 more years**. If you have no trouble coughing well now, you won't have any trouble for about 10 more years. If you have mild trouble with coughing now, it will not get worse for about 10 more years. If you have a weak cough now, it will not get worse for about 10 more years.
- **"Cough strength: maintained for 2 years."** This means that your cough would stay at the current level for an average of **2 more years.**
- **"Cough strength: no benefit."** The drug would not work on your coughing at all, so your cough would weaken over time.

Lung Infections

Taking the medicine may help you get fewer infections in his lungs. Getting an infection in the lungs means you have to go to the doctor and take antibiotics. Serious infections like pneumonia have to be treated in the hospital, and they might make it harder for your lungs to work well over time. Here are ways that the medicine could help with lung infections:

- **"Lung infections: very few."** After you start taking the drug, you would get lung infections very rarely, if at all, for your whole life.
- **"Lung infections: half as many."** After you start taking the drug, you would get about half as many lung infections compared to if you did not take the drug.
- **"Lung infections: no benefit."** The drug would not affect how often you get lung infections.

Mild Diarrhea

Because of taking the medicine you may get mild diarrhea. This means that you have **2 to 4 more bowel movements a day**, but you do not have to go to a doctor for it. The diarrhea may last only a few days. Taking the medicine may cause:

No (or 0%) extra chance you will get **diarrhea**.
1 out of 5 (or 20%) chance you will get **diarrhea**.
1 out of 2 (or 50%) chance you will get **diarrhea**.

Blood Tests

Because of taking the medicine, **for the whole time you are treated** you will have to have blood tests for safety. Your doctor may ask for:

No blood tests. This means you do not have to have any extra blood tests during the year.
Blood tests 2 times a year. This means you have extra blood tests every 6 months.
Blood tests 4 times a year. This means that you have extra blood tests every 3 months.

Task 2.

It is time to start the second task. You will see 9 different treatments. Some parts of the treatments used in this survey are real but other parts are made up. We are interested in knowing what you would choose if these treatments did exist. There are no right or wrong answers. Remember, we are imagining that these are approved treatments provided by the doctor, and **not** treatments given during a clinical trial. These treatments are in addition to any medications you currently take, and will not replace those medications. Please assume that all of the medical bills, including the cost of the treatments, are covered by health insurance.

To make the task work, a computer chose a set of benefits and risks. Some of the treatments may not seem realistic. For example, sometimes the treatments sound bad. Even though this may feel wrong, it is important to make the task work. Please answer the questions as well as you can.

Some people find this task difficult. Feel free to take a break. Nobody is going to know if you stop, and we want you to be comfortable. After a break you can come back to the survey, as long as you are using the same computer. If you have questions or concerns about this survey, please contact Holly Peay at holly@parentprojectmd.org.

Example task

Here is an example. Mike is taking the survey. He sees this table describing several effects of the treatment.

Best		Worst
X	Cough strength: Maintained for 10 years	O
O	Lung infections: Half as many	O
O	Mild diarrhea: 1 in 5 (20%)	X
O	Blood test: 4 times a year	O

This table shows a treatment that has two benefits: cough strength is maintained for 15 years, and there are half as many lung infections as expected. But there are downsides. There is a 20% chance of diarrhea, and people who take the drug have a blood draw 4 times a year to test for safety.

Mike has to pick the best and worst things about the drug. It was hard to pick the best thing, because he believes that “cough strength maintained for 10 years” and “half as many lung infections” are both very good. Mike clicked on the circle next to “cough strength: maintained for 10 years” because he decided it was best. Mike was worried about the “20% chance of diarrhea” and the “blood draws 4 times a year,” but he clicked the circle next to “20% chance diarrhea” because he thought it would be the worst thing about using the treatment.

Now it is your turn. For each treatment we describe, choose the best and worst thing. Then tell us whether you think you would decide to use the treatment for yourself. You will find a reminder of the directions above each table.

[on each screen: Choose the best thing about the treatment by clicking the circle under “Best” and choose the worst thing by clicking the circle under “Worst.” You have to choose a best and a worst thing to move on. Remember that a computer chose combinations to make the task work, and some of them seem bad. Even so, please pick the best and worst thing.

There are no right or wrong answers. We are interested in your honest opinions. If you have questions or concerns about this survey, please contact Holly Peay at holly@parentprojectmd.org.]

Best		Worst
O	Cough strength: No benefit	O
O	Lung infections during your life: Half as many	O
O	Your chance for diarrhea: No extra chance	O
O	How often you need a blood test: 4 times a year	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: No benefit	O
O	Lung infections during your life: Very few	O
O	Your chance for diarrhea: 1 in 5 (20%)	O
O	How often you need a blood test: 2 times a year	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: Maintained for 2 years	O
O	Lung infections during your life: Very few	O
O	Your chance for diarrhea: 1 in 2 (50%)	O
O	How often you need a blood test: 4 times a year	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: Maintained for 10 years	O
O	Lung infections during your life: Very few	O
O	Your chance for diarrhea: No extra chance	O
O	How often you need a blood test: No extra blood tests	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: Maintained for 2 years	O
O	Lung infections during your life: No benefit	O
O	Your chance for diarrhea: No extra chance	O
O	How often you need a blood test: 2 times a year	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: Maintained for 10 years	O
O	Lung infections during your life: No benefit	O
O	Your chance for diarrhea: 1 in 5 (20%)	O
O	How often you need a blood test: 4 times a year	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: Maintained for 10 years	O
O	Lung infections during your life: Half as many	O
O	Your chance for diarrhea: 1 in 2 (50%)	O
O	How often you need a blood test: 2 times a year	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: No benefit	O
O	Lung infections during your life: No benefit	O
O	Your chance for diarrhea: 1 in 2 (50%)	O
O	How often you need a blood test: No extra blood tests	O

Would you choose to use this treatment? YES / NO

Best		Worst
O	Cough strength: Maintained for 2 years	O
O	Lung infections during your life: Half as many	O
O	Your chance for diarrhea: 1 in 5 (20%)	O
O	How often you need a blood test: No extra blood tests	O

Would you choose to use this treatment? YES / NO

You are now finished with the second task.

Task 3.

These are the last questions and they should take less than 10 minutes. In the tasks you just completed, we only asked for your input on a few items. There are lots of other benefits, side effects, and details about how a medicine is taken.

Imagine a medication described below. In your own opinion, how meaningful are the following medication benefits and risks to you?
[Order of items below will be randomized].

People with DBMD have progressive loss in lung function when they get older. This means they have to use devices like cough assist or BiPAP to support breathing during the day and sometimes also during the night. If the medication could slow down your loss in lung function for 5 more years, would this be important for you?

Not at all / A little / Somewhat / Very much

If the medication could maintain your ability to cough well for 5 more years, how important is that to you?

Not at all / A little / Somewhat / Very much

If the medication caused you to have fewer lung infections over the next 5 years, how important is that to you?

Not at all / A little / Somewhat / Very much

The medication comes as small, coated pills that would be taken 3 times a day. For each dose you would take 2 pills—a total of 6 pills each day. The medication needs to be taken with food and it cannot be crushed. Most people find it easy to swallow and it has no taste. How much of a burden is this for you?

Not at all / A little / Somewhat / Very much

For the whole time you take the medicine, you would need blood tests every six months (twice a year). How much of a burden is this for you?

Not at all / A little / Somewhat / Very much

Because of taking the medication, you could have mild and temporary diarrhea as a side effect. How much of a burden is this for you?

Not at all / A little / Somewhat / Very much

You finished the third task and completed the entire survey. Thank you for your time.

Curriculum Vitae

Ilene L. Hollin, MPH
PhD Candidate

PERSONAL DATA

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CONTACT INFORMATION

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EDUCATION

Doctor of Philosophy (PhD) in Health Economics and Policy
Johns Hopkins Bloomberg School of Public Health — Baltimore, MD
Department of Health Policy and Management
Advisor: John F.P. Bridges, PhD
Certificate in Public Health Informatics

Master of Public Health (MPH) — 2007-2009
Columbia University Mailman School of Public Health — New York, NY
Effectiveness and Outcomes Research

Bachelor of Arts (BA) — 2001-2005
Brandeis University — Waltham, MA
Majors: American Studies, International Studies; Minor: Journalism

FELLOWSHIPS & AWARDS

- Isaac and Catharine Hecht Scholarship, Central Scholarship, 2015
- Alison Snow Jones Memorial Prize, Bloomberg School of Public Health, 2015
- Charles D. Flagle Award, Bloomberg School of Public Health, 2014
- Lee Lusted Student Prize in Decision Psychology and Shared Decision Making, Society for Medical Decision Making (SMDM), 2013
- Cross-Center Research Fellow, Johns Hopkins Center to Eliminate Cardiovascular Disparities and Centers for Population Health and Health Disparities, 2013-2014
- Training Grant Fellow, Division of Health Sciences Informatics, 2011-2013
- *Magna Cum Laude*, Brandeis University, 2005

CURRENT RESEARCH EXPERIENCE

Bloomberg School of Public Health, Roger Lipitz Center for Integrated Health Care
Center Director: Karen Davis, PhD
Graduate Research Associate
2014 - Present

Bloomberg School of Public Health, Stated Preference Study Team
Faculty: John F.P. Bridges
Graduate Research Associate
2012 - Present

PREVIOUS RESEARCH EXPERIENCE

US Department of Health and Human Services, Office of the National Coordinator (ONC) for Health Information Technology
Office of Planning, Evaluation, and Analytics
Program Specialist
2012 - 2015

Cincinnati Children's Hospital, Collaborative Chronic Care Network (C3N)
PIs: Michael Seid and Peter Margolis
Project Leadership Team Member; Workgroup Lead for C3N for cystic fibrosis
2014 - 2015

Bloomberg School of Public Health, **Center to Eliminate Cardiovascular Disparities**
Project ReDCHiP (Reducing Disparities and Controlling Hypertension in Primary Care)
PIs: Lisa Cooper, MD MPH and Jill Marsteller, PhD
Research Assistant
2012 - 2014

Johns Hopkins University, Department of Medicine
Impact of healthcare costs
PI: Karen Robinson, PhD
Research Assistant
2013

Healthcare Innovation and Technology Lab
Research Manager
2009-2011

New York Presbyterian Hospital, Quality and Patient Safety
Virtual Pediatric Intensive Care Unit
Research Assistant
2008-2009

New York State Psychiatric Institute/Columbia University, Child Advanced Center for Intervention and Services Research
Coordinator
2006-2008

OTHER PROFESSIONAL EXPERIENCE

Ruder Finn, Corporate Technology Practice
Account Executive
2005-2006

TEACHING EXPERIENCE

Bloomberg School of Public Health, Department of Health Policy and Management
Introduction to Health Economics with Douglas Hough, PhD
Lead Teaching Assistant, January – March 2014 and January – March 2015

Public Health Policy with Gerard Anderson, PhD
Teaching Assistant, July - August 2014

Introduction to the US Healthcare System with Bradley Herring, PhD
Teaching Assistant, October – December 2013

Introduction to Health Policy with Gerard Anderson, PhD
Teaching Assistant, August – October 2012 and August – October 2013

Research and Evaluation Methods in Health Policy with Daniel Webster, PhD and Renan Castillo, PhD
Teaching Assistant, March 2013 - May 2013

Health Economics III with John Bridges, PhD
Teaching Assistant, March 2013 - May 2013

Economic Evaluation I with Kevin Frick, PhD
Teaching Assistant, October – December 2012

Bloomberg School of Public Health, Department of International Health
Economic Evaluation II with Dagna Constenla, PhD and Kevin Frick, PhD
Teaching Assistant, January – March 2013

PROFESSIONAL MEMBERSHIP

AcademyHealth, 2012- Present
Society for Medical Decision Making, 2012 – Present
International Society For Pharmacoeconomics and Outcomes Research, 2015 - Present

COMMITTEE MEMBERSHIP

Bloomberg School of Public Health, Department of Health Policy and Management
Honors and Awards Committee, 2013-2014
Public Health Practice Committee, 2012-2013

PEER REVIEW ACTIVITIES

2015- Present	**Ad hoc reviewer** for *Value in Health*
2010- Present	**Ad hoc reviewer** for *Cost Effectiveness Analysis Registry,* Tufts Medical Center, Center for the Evaluation of Value and Risk in Health

GRANT FUNDING

Cystic Fibrosis Foundation (2015): "Economic Analysis of Long-Term Cystic Fibrosis Costs." ($58,600)

PUBLICATIONS

Original Articles in Peer-Reviewed Journals

- **Hollin IL**, Young C, Hanson C, Bridges JF, Peay HL. Developing a patient-centered benefit-risk survey: a community-engaged approach. *Value in Health*. Forthcoming.
- **Hollin IL**, Robinson K. Economics of cystic fibrosis: a scoping review and gaps analysis. *Applied Health Economics and Health Policy*. 2016;14(2)151-159.
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- **Hollin IL**, Peay HL, Bridges JF. Caregiver preferences for emerging Duchenne muscular dystrophy treatments: a comparison of best-worst scaling and conjoint analysis. *The Patient*. 2015;8(1):19-27.
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- **Hollin I**, Griffin M, Kachnowski S. How will we know if it's working? A multi-faceted approach to measuring usability of a specialty-specific EMR. *Health Informatics Journal*. 2012 Sept; 18(3):219-232.
- Dhar M, Griffin M, **Hollin I**, Kachnowski S. Innovation spaces: Six strategies to inform healthcare. *The Healthcare Manager*. 2012;31(2):166-177.
- Seegert L, **Hollin I**, Kachnowski S. Information technology use in the patient-centered medical home: An assessment and discussion. *Journal of Healthcare Information Management*. 2011;25(2):40-45.
- Vidair H, Reyes J, Shen S, Parrilla-Escobar M, Heleniak CM, **Hollin I**, Woodruff S, Turner JB, Rynn M. Screening parents bringing their children for psychiatric evaluation: Exploring parent and child psychopathology in the same clinic. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2011;50(5):441-450.

- Wei J, **Hollin I**, Kachnowski S. A review of the use of mobile phone text messaging in a clinical and health behaviour intervention. *Journal of Telemedicine and Telecare*. 2011;17:41-48.

- Edwards A, **Hollin I**, Barry J, Kachnowski S. Barriers to cross institutional health information exchange: A literature review. *Journal of Healthcare Information Management*. 2010;24(3):22-34.

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- **Hollin IL**, Bridges JF, Peay H. Patient-centered benefit-risk assessment in Duchenne Muscular Dystrophy. Under Review.

- **Hollin IL**, Davis K, Nicholas L, Schoen C, Willink A, Wolff J. Functional limitations of Medicare beneficiaries and health care spending: need for new policy strategies. Under Review.

- Schoen C, Davis K, Buttorff C, **Hollin I**, Nicholas L. Modernizing Medicare's Benefits to Meet the Needs of Beneficiaries - Especially Low- Income, Complexly Ill Beneficiaries. Under Review.

Working Papers

- **Hollin IL**, Peay H, Bridges JFP. Caregiver and Patient Preferences of Treatment Targets: An Example for Duchenne and Becker Muscular Dystrophy Using Latent Class Analysis. Working Paper.

- **Hollin IL**, Lee W, Patel V. Pioneer ACO Health IT Capabilities: Progress and performance toward Meaningful Use. Working Paper.

- **Hollin IL**, Patel V, King J, King J, Buntin M. Clinical benefits of electronic health records: changes in physician perception. Working Paper.

Other Reports and Articles

- Moon M, **Hollin IL**, Nicholas LH, Schoen C, Davis K. Serving older adults with complex care needs: a new benefit option for Medicare. The Commonwealth Fund, July 2015.

- Heisey-Grove D, Hufstader M, **Hollin I**, Samy L, Shanks, K. Progress towards the meaningful use of electronic health records among critical access and small rural hospitals working with Regional Extension Centers. ONC Data Brief, no. 5. Washington, DC: Office of the National Coordinator for Health Information Technology, November 2012.

POSTER PRESENTATIONS

- **Hollin IL**, Camponeschi G, Paly VF, Mao T, Danoff S, Bridges JF. Developing a patient-centered instrument for treatment preferences in idiopathic pulmonary fibrosis. Poster presentation at: Pulmonary Fibrosis Foundation Summit 2015: From Bench to Bedside; 2015 Nov 12-14; Washington, DC.

- **Hollin IL**, Young C, Hanson C, Bridges JF, Peay H. Developing a stated-preferences instrument for Duchenne/Becker muscular dystrophy– A community-engaged research application. Poster presentation at: The 37th Annual Meeting of the Society for Medical Decision Making; 2015 Oct 18-21; St. Louis, MO.

- **Hollin IL**, Young C, Hanson C, Bridges JF, Peay H. Stated-preference survey development for muscular dystrophy–A community-engaged research application. Poster presentation at: The 3rd Meeting of the International Academy of Health Preference Research; 2015 Oct 18; St. Louis, MO.

- **Hollin IL**, Lee W, Patel V. Pioneer ACO Health IT Capabilities: Progress and performance toward Meaningful Use. Poster presentation at: 2015 AcademyHealth Annual Research Meeting; 2015 June 14-16; Minneapolis, MN.

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