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ORIGINAL RESEARCH ARTICLE

How Do Members of the Duchenne and Becker Muscular Dystrophy Community Perceive a Discrete-Choice Experiment Incorporating Uncertain Treatment Benefit? An Application of Research as an Event

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Abstract

Background Best–worst scaling methods have been used in several Duchenne and Becker muscular dystrophy (DBMD) studies to quantify patient and caregiver priorities and preferences and promote patient-focused drug development (PFDD). We sought to assess the extent to which different members of the DBMD community would accept a discrete-choice experiment (DCE) that incorporates uncertainty regarding individual-level benefit.

Methods A community advisory board encouraged the development and testing of a DCE to further examine treatment preferences in DBMD and to facilitate the inclusion of a policy-relevant uncertainty attribute. The DCE assessed preferences across a primary outcome (muscle strength) and several risks (uncertainty regarding treatment benefit, kidney damage risk, and fracture risk). The single instrument was tested among adult patients, caregivers, and professionals at the national Parent Project Muscular Dystrophy annual meeting. The DCE was analyzed using conditional logit. Instrument acceptability was evaluated using a previously developed set of questions assessing ease of understanding and answering, and if answers reflected the respondents' real preferences. We proposed a 75% agreement rate as a threshold of acceptability, and used a Z score to assess if this was met, exceeded, or rejected.

Results A total of 161 people completed the survey including 9 patients, 87 caregivers, and 65 professionals. Patients reported high acceptability across all evaluation items (p values > 0.21). Caregivers and professionals exceeded the benchmark of acceptability on understanding and reflecting real preferences ($p < 0.001$). Professionals met the benchmark ($p = 0.08$) for ease of answering, but caregivers did not ($p < 0.01$). DCE results demonstrated that all groups made meaningful trade-offs, with patients being less tolerant of risks than either caregivers or professionals ($p < 0.001$), and with no significant difference between caregivers and professionals ($p = 0.46$).

Conclusions This study demonstrates the acceptable application of a single instrument across a multi-stakeholder population that used a complex preference method and included a policy-relevant uncertainty variable. Ease of answering was lowest among caregivers, but a post-hoc analysis revealed that it was most difficult for those with children under the age of 10, while those with older children met the threshold. The success of this study has laid the foundation for a global study of DBMD preferences using this method.

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Key Points for Decision Makers

Numerous patient and caregiver preference studies have been conducted in partnership with the Duchenne and Becker muscular dystrophy (DBMD) community using best–worst scaling methods. Our community advisory board challenged us to demonstrate that the techniques used in other benefit–risk studies could be used in DBMD.

To test the feasibility of diverse community participation in a DCE, patients, caregivers, and professionals completed a survey measuring benefit–risk trade-offs for experimental treatments at an advocacy event where social and logistical supports were readily accessible.

Participants completed the DCE without report of harm or significant challenge. Given its suitability and acceptability, a DCE will be used in a future international study assessing treatment preferences for DBMD.

1 Introduction

Quantitative measures of patient preferences are increasingly being embraced by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as tools to inform regulatory benefit–risk decisions and promote patient-focused drug development [1, 2]. Such methods allow incorporation of perspectives from large samples, which increases the representativeness and inclusiveness of the results over more traditional testimony approaches [1, 3]. Quantitative methods also provide an opportunity for researchers to explore heterogeneity of the target population [4]. Recent guidance by the FDA documents the merit of considering preference evidence when assessing the benefit and risk profile of a treatment under review [5, 6].

Through an ongoing partnership, the Duchenne and Becker muscular dystrophy (DBMD) community and researchers have created a stakeholder engagement approach involving patients and caregivers in developing patient-centered instruments using techniques such as best–worst scaling [7–9]. These efforts have generated frameworks and case studies in community engagement and have resulted in preference results to advise the FDA and industry sponsors [8, 10–12].Various stated-preference techniques such as best–worst scaling and conjoint analysis have been used to elicit patient and caregiver preferences in the DBMD community to promote patient-focused drug development [13–15]. This work has indicated that muscle benefit (more so than life prolongation) is the most desired attribute of emerging DBMD treatments, and that community members are willing to trade improvements in muscle function in exchange for a chance of serious risks such as bleeding and heart arrhythmia [15].

Although discrete choice experiments (DCEs) have been applied in healthcare settings [16–18] and diverse rare disease contexts [19–21], methods experts/industry advisory committee members (see acknowledgements for full list) were particularly interested in whether the approach could be efficiently employed in their unique community, and whether the same instrument could be used to collect and compare perspectives of diverse groups including patients, caregivers, and professionals. Research authors and advisory committee members weighed the desire to conduct rigorous DCEs against the feasibility of doing so, as DCEs can be cognitively burdensome to the respondent [22], which made stakeholders (including patients, families, researchers, and advocates) hesitant to use them in previous studies [9]. In addition, research authors had concerns about scenario rejection (i.e., that participants would not complete the instrument) if the same DCE instrument was used for patients, parents, clinicians, and industry stakeholders. A 'proof of principle' approach [23] was therefore taken to understand whether DCEs could be feasibly completed without scenario rejection among diverse members of the DBMD community.

There is a lack of evidence demonstrating the acceptability and suitability of these methods. Understanding how patients, caregivers, and professionals interact with such instruments is crucial to future dissemination and implementation of these methods in the DBMD community.

2 Methods

2.1 Community Engagement

We employed a community-centered approach to ensure that the study was patient-centered and relevant; however, given the exploratory nature of this study and our experience from our recent work in the DBMB community, we included fewer rounds of input and review than previous processes [9]. A community advisory board was brought in to oversee the study and to minimize adverse events such as psychological harm or discontent. The board comprised one parent, one patient, one clinician, two members of industry, one member of an umbrella rare-disease patient group, and one social scientist. Multiple phone conferences were conducted to explain the study approaches, communicate the benefits and challenges of such innovative approaches, and adjust the study design based on input from the community advisory board. Two additional caregivers participated in think-aloud phone interviews to assess comprehension, refine terminology, and explore the usability of the instrument. Their input was used to finalize the instrument.

2.2 Research as an Event

To address the community concerns about the DCE method, we conducted this study to allow direct interaction with respondents (if needed) during data collection. Thus, we recruited and engaged respondents at the Parent Project Muscular Dystrophy (PPMD) annual meeting and offered social and logistical support from both researchers and PPMD staff.

In this way, we used a 'research as an event' approach by having PPMD actively inform, recruit, and support data collection. Research as an event is a pragmatic methodology that connects researchers and the disease community at events not primarily convened for research. These events can be used for recruiting and engaging stakeholders to participate in research activities in supportive environments. Research as an event approaches demonstrate a research team's willingness to be community centered [8, 24, 25] and are particularly beneficial for feasibility testing as they allow both community partners and researchers to act as a real-time help desk.

The recruitment strategy was adapted to be appropriate for the structure of the event. Paper surveys were included in the registration package to reach maximal participants at their convenience [26] because it could not be assured that participants would have access to internet-compatible devices. An electronic version of the survey was also available through an online survey platform. The study team communicated their preference for use of the paper survey for all participants who were able to complete the paper version. Teens and adults with DBMD who were no longer able to easily manipulate paper and pen were invited to use the online survey.

PPMD staff members gave several reminders about completing the survey between the educational sessions. Conference attendees were eligible to participate if they self-identified as (1) a patient with DBMD over 18 years old; (2) a caregiver of a DBMD patient (this caregiver could be a parent, grandparent, or legal guardian); or (3) a healthcare professional or industry representative. Professionals from diverse backgrounds were collapsed into a single category as they had high medical knowledge about DBMD, but did not have lived experience with the disease. The survey encouraged participants to contact any one of four individuals from PPMD or the research team (HP, RF, JT, EJ) if they had questions, comments, concerns, or needed further help. If patients requested help from caregivers to physically complete the survey, study staff clarified that all survey answers should come from the patient rather than the caregiver.

2.3 Survey Development and Design

We employed a DCE to examine the trade-offs between adverse events and treatment benefits. DCEs use attributes, or characteristics, to describe the treatment profiles. The respondents are asked to make a selection between two or more profiles with different attribute levels. Based on repeated choices, the researchers can estimate the trade-offs people are willing to make between each attribute [16–18, 27, 28].

We developed a novel DCE using a vignette focused on clinical-trial benefit and risk data presented in comparison with placebo. Respondents were asked to consider which drugs were "better for people with DBMD" based on hypothetical clinical trial data. This judgement-based elicitation was selected as it was relevant to not only patients and caregivers but also to professionals, who might be involved in, but not make, treatment decisions.

Respondents considered hypothetical clinical trial data of a treatment designed to improve muscle strength, a treatment benefit valued by the DBMD community [8, 9, 13–15, 29, 30]. The benefits and risks included in the hypothetical treatments were selected after discussions with the community advisory board and based on past study evidence. Muscle benefit, the primary outcome, was described qualitatively, and the three levels were defined as (1) small but potentially meaningful improvement in muscle strength when compared with placebo, (2) medium improvement in muscle strength when compared with placebo, and (3) large improvement in muscle strength when compared with placebo.

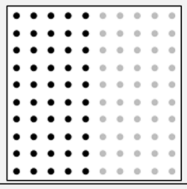
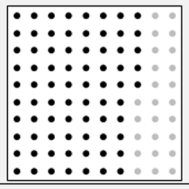
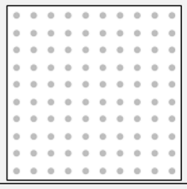
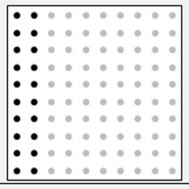
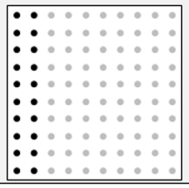
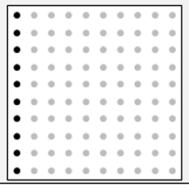
The risks included the probability that the treatment would have an additional risk of kidney damage (no additional risk,10% higher risk, 20% higher risk) compared with a placebo, and have an additional risk of fracture (no additional risk, 10% higher risk, 20% higher risk) compared with a placebo. In addition, we included a policy-relevant attribute about treatment uncertainty; that the treatment may not work for any particular individual (25% chance, 50% chance, 75% chance). Treatment uncertainty is a major consideration in drug development and approval and was a particularly timely regulatory issue when the survey was conducted; it has also not been previously explored in DBMD preference studies.

Outcomes of the hypothetical experimental medication were described as occurring after 12 months of treatment under a clinical trial, compared with taking a placebo. The survey vignette and attribute labels highlighted that increased risk of fracture and kidney damage were relative to a placebo, rather than about absolute risk.

A D-efficient experimental design was used to generate 12 choice tasks in Ngene (ChoiceMetrics 2012, Ngene 1.1.1 user manual & reference guide, Australia) [31, 32]. Each attribute level appeared an equal number of times on the

Fig. 1 Example of the choice task

Task 1: Based on your own opinion, which is the better drug?

	Drug A	Drug B
Is there muscle benefit?	Small improvement	Large improvement
How many people would benefit?	50% 	75% 
What is the risk of kidney damage?	No additional risk 	20% higher risk 
What is the extra fracture risk?	20% higher risk 	10% higher risk 
In your opinion, which is the better drug?	☐	☐

12 choice tasks [33]. In designing the DCE instrument, we adopted pictographs (risk grids) to communicate the effect of risks [34]. Participants were then asked to view two side-by-side pictographs, each of which depicted a drug. Based on the information presented in this pictograph, participants were asked to indicate which drug they thought was better for people with DBMD (Fig. 1). The current study used a pragmatic approach in framing risks, and did not include an opt-out choice (as we intended to report trade-offs rather than thresholds) or utility specification. Excluding these features is consistent with prior work in diverse medical contexts [35]. As the surveys were primarily completed on paper, there was only one fixed version of the experiment.

Prior to completing the DCE, respondents also provided descriptive demographic information including age, country of citizenship, and type of health insurance, as well as disease context information such as diagnosis (Duchenne muscular dystrophy or Becker muscular dystrophy) and history of fractures. Familiarity with the drug development process and FDA was assessed using a four-point Likert scale (ranging from not at all familiar to very much familiar). The final question of the survey solicited open-ended feedback by instructing respondents, "If you have any comments or questions, please write them here". Among individual's pretesting the instrument, feedback indicated that the DCE was clearly presented. Several phrases and terms were modified to better reflect terminology familiar to patients and families, but the nature or structure of the survey was largely unchanged.

2.4 DCE Acceptability Assessment

Consistent with International Society for Pharmacoeconomics and Outcomes Research guidance on good research practices for conjoint analysis in health care [36], acceptability of the DCE was assessed. Despite recommendations to measure acceptability or confidence in choices, there are not well established or systematic methods by which to do so. Researchers often qualitatively confirm participant's acceptability of the instruments through pilot testing (see [37] for an example of this).

Participants were asked to indicate their level of agreement with the following three statements assessing the acceptability of the DCE (Fig. 2): (1) "I found it easy to understand the questions", (2) "I found it easy to answer the questions", and (3) "My answers showed my real preferences". We then explored whether the instrument was acceptable, defined as 75% agreement with each statement. This threshold was based on a previous national study that

These statements refer to the questions about the made-up drugs that you just answered. Please mark your answers in the grid.

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
I found it easy to **understand** the questions	☐	☐	☐	☐	☐
I found it easy to **answer** the questions	☐	☐	☐	☐	☐
My answers showed my real preferences	☐	☐	☐	☐	☐

Fig. 2 Discrete-choice experiment acceptability questions

found 64–80% agreement with these items [38]. *Z* scores describing the difference between respondent agreement with the 75% threshold were calculated and assessed with two-tailed tests.

Participants also rated the following four personality statements on a five-point Likert scale: (1) "I am always optimistic about my future", (2) "I am actively working to improve my health", (3) "I am a risk taker", and (4) "I am good with numbers". Differences in personality between groups were assessed using descriptive statistics and ANOVA.

2.5 Statistical Analysis

Conditional logit was used to construct aggregated and stratified models for the three participant populations (patient, caregiver, and professional) [39]. All attributes were checked for violations to monotonicity. Variables were treated as continuous, as this approach produces more parsimonious estimators. Parsimony benefits communication with external audiences and is applicable for a community-centered modeling approach wherein results can be meaningfully translated to patients and caregivers. This approach is consistent with previous research [40, 41]. We developed and analyzed the 'chance of benefit' attribute as a risk variable representing uncertainty in treatment, and recoded the chance of benefit as negative and renamed the attribute 'failure rate.'

Preferences for the aggregated and stratified models were estimated using maximum acceptable risk (MAR) with standard errors estimated using the delta method in Stata version 14 (StataCorp, College Station, TX, USA). The MAR measure was calculated by dividing the coefficient of the benefit (from conditional logit modeling) by the coefficient for each risk. A Wald test assessed differences in preferences between respondent types. The Swait-Louviere test assessed whether identified differences were due to scale heterogeneity [42, 43]. Interactions were not assessed, as we had no a priori hypotheses regarding interactive effects.

Table 1 Characteristics of participants ($n = 161$)

Participant characteristics	Mean (SD) or %
Participant	
Patient age, years	23.7 (4.5)
Caregiver age, years	44.8 (9.8)
Professional age, years	45.7 (11.5)
Patient	
DBMD diagnosis	
Duchenne	89%
Becker	11%
Caregiver	
Relationship to DBMD patient[a]	
Mother	87%
Father	8%
Other legal guardian	2%
Professional	
Role[b]	
Clinician	29%
Researcher	35%
Biopharmaceutical	40%
Other	15%
Patient and caregiver	
Bone fracture experience[a]	
Yes	32%
No	58%
Insurance[b]	
Private	77%
State/government	29%
Other	3%

DBMD Duchenne and Becker muscular dystrophy

[a]Does not add to 100% due to missing data

[b]All that apply. Responses may add to more than 100%

3 Results

3.1 Descriptive Statistics

A total of 164 respondents completed the survey with a response rate of 39% (out of 425 surveys distributed at the conference). Three respondents who did not complete the screening questions or did not qualify based on the screening questions were excluded, leaving a total of 161 respondents (9 patients, 87 caregivers, and 65 professionals) in the final analytic sample (Table 1). Patients, caregivers, and professionals had a median age of 23.7, 44.8, and 45.7 years, respectively. The majority of respondents (93%) originated from the US, while the remaining participants came from Australia, Asia, or Europe. Almost three-quarters of respondents (71%) rated themselves as somewhat or very familiar with the drug development process and the FDA.

The large majority (90%) of patients and caregivers indicated that the diagnosis of the affected person with DBMD was Duchenne muscular dystrophy. Most (77%) of the patients and caregivers used private health insurance to support their treatment for DBMD. Most caregivers (87%) were biological mothers of a DBMD family member. Slightly more than half of the patients had not experienced a broken bone (58%), and two-thirds (66%) had used corticosteroids.

3.2 DCE Acceptability

The majority of patients, caregivers, and professionals found the single instrument easy to understand (78%, 89%, 92%, respectively; Table 2) and answer (67%, 60%, 65%), and agreed that their answers showed their real preferences (89%, 89%, 95%). Each of the three groups met or exceeded the 75% agreement threshold for the acceptability measures. The only exception to this was among caregivers, who were significantly less likely to agree that the questions were easy to answer in comparison with the 75% threshold (60%, $p < 0.001$).

Patients, caregivers, and professionals were equally likely to endorse themselves as health seeking, risk taking, and good with numbers (all between-group p values > 0.05; Table 3). Caregivers were less likely to agree that they were optimistic (mean 0.86, SD 0.80) compared with patients (mean 1.22, SD 0.83) and professionals (mean 1.23, SD 0.64, $p = 0.01$).

3.3 Treatment Preferences

Results of the conditional logit model are presented in Table 4. When aggregated, respondents valued all treatment attributes ($p < 0.001$), including muscle strength, uncertainty about drug benefit, risk of kidney damage, and risk of fracture. Respondents favored an improvement in muscle strength (Coeff. 0.879, SE 0.05), and wanted to avoid an increase in uncertainty about benefit (Coeff. −0.040, SE 0.002), increased risk of kidney damage (Coeff. −0.097, SE 0.005), and increased risk of bone fracture (Coeff. −0.034, SE 0.005).

When stratified by respondent role (patient, caregiver, and professional), the direction of the preference result remained similar to that of the aggregated conditional logit model. When comparing separate models using the Wald test, the patient model was statistically different to that of the caregiver and the professional ($p < 0.001$) [43]. The preference result of the caregiver and the professional model showed

Table 2 Test of acceptability of discrete-choice experiment

Acceptability items	Patients ($n = 8$)		Caregivers ($n = 86$)		Professionals ($n = 64$)	
	Z score[a]	p value[b]	Z score[a]	p value[b]	Z score[a]	p value[b]
Easy to understand	0.19	0.85	3.93	< 0.0001	5.20	< 0.0001
Easy to answer	0.50	0.62	−2.88	< 0.01	−1.74	0.08
Real preferences	1.25	0.21	3.93	< 0.0001	7.77	< 0.0001

[a]Reflects comparison between % agree or strongly agree as compared to desired 75% agreement threshold

[b]Significance of two-tailed test

Table 3 Mean Likert rating for personality characteristics

Personality characteristics	Patients $n = 9$ Mean (SD)	Caregivers $n = 86$ Mean (SD)	Professionals $n = 64$ Mean (SD)	p value
I am always optimistic about my future	1.22 (0.83)	0.86 (0.80)	1.23 (0.64)	0.01
I am actively working to improve my health	1.11 (0.60)	1.0 (0.74)	1.25 (0.64)	0.10
I am a risk taker	−0.11 (1.17)	0.33 (1.01)	0.41 (1.01)	0.36
I am good with numbers	1.0 (1.12)	0.74 (1.00)	1.03 (0.93)	0.20

5-point Likert scale, −2 to 2, strongly disagree to strongly agree

Table 4 Preference coefficient estimates from discrete-choice experiment (DCE)

	Patients		Caregivers		Professionals	
	Coefficient	SE	Coefficient	SE	Coefficient	SE
Muscle strength[a]	0.55**	0.26	0.88**	0.07	0.93**	0.08
Failure rate[b]	−0.08**	0.02	−0.04**	0.003	−0.04**	0.004
Risk of kidney damage[b]	−0.15**	0.04	−0.10**	0.01	−0.09**	0.01
Risk of fracture[b]	−0.07**	0.03	−0.03**	0.01	−0.04**	0.01
Pseudo log likelihood	−30.26 ($p=0.00$)		−421.13 ($p=0.00$)		−324.72 ($p=0.00$)	

		Chi^2 statistics	*p* value
Wald test	Patients vs caregivers	24.81	0.0001
	Patients vs professionals	27.33	<0.0001
	Parents vs professionals	3.64	0.46

SE standard error; results obtained using conditional logit

[a]Measuring units: one step improvement

[b]Measuring units: additional 1%

*$p<0.05$, **$p<0.001$

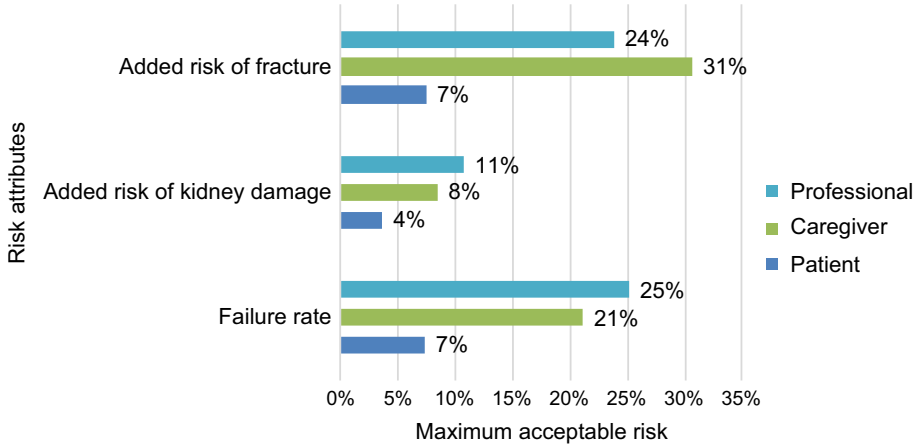


Fig. 3 Maximum acceptable risk for a one-level improvement in muscle benefit

no statistical difference ($p=0.46$). Any differences in the preference results were not attributable to scale ($p<0.001$), as concluded from the Swait–Louviere test [42].

MAR was used to compute the trade-offs respondents were willing to make between treatment benefit (muscle benefit) and treatment harms, as depicted in Fig. 3. Aggregated results indicated that the MAR for improved muscle function could be described in terms of a 22% increase in uncertainty about drug benefit ($p<0.001$), a 9% risk of kidney damage ($p<0.001$), or a 26% increase in fracture risk ($p<0.001$).

4 Discussion

Findings from our event-based research demonstrates that patients, caregivers, and professionals have identifiable preferences for emerging DBMD treatments that can be suitably elicited using the stated-preference method of DCE. Instrument endorsement by diverse stakeholders and presentation of results using patient-friendly and policy-relevant metrics such as MAR provides evidence that DCE approaches are feasible for the DBMD stakeholder community. The FDA has cited MAR as a tool to help inform benefit and risk considerations of patient preference information [5]. We believe that MAR is more intuitive and easier to interpret than traditional preference results, and can be more easily communicated to the public and regulatory officials. Improving risk communication and health literacy are ongoing priorities at the FDA [44]. These responses represent a 'proof of concept' demonstrating that advanced stated-preference methods such as DCE can be feasibly and acceptably used to directly capture the perspectives of people with DBMD and other stakeholders [9], even when using the same instrument with all stakeholders.

That the majority of participants in three groups found the instrument easy to understand, easy to answer, and

consistent with their preferences is a positive indicator that DCEs can be meaningfully used by the DBMD community. The finding that caregivers had a more difficult time answering the DCE led us to conduct an exploratory analysis of this group, which suggested that age of the caregiver's child with DBMD drove difficulty in answering questions; caregivers of children with DBMD aged 10 years or older ($n=29$) met the threshold ($p=0.54$), while parents of children younger than 10 years ($n=53$) did not ($p<0.001$).

Difficulty in answering the questions among caregivers of younger children may stem from parents having had psychological and/or cognitive challenges when thinking ahead to a future loss. Previous preference research in DBMD has opted to exclude caregivers of boys under 10 years due to fear of scenario rejection, as well as due to an incident wherein a parent of a young child experienced psychological upset from completing the tasks [9]. Parents of younger boys accepted the scenario in the current work, answering in a way that was consistent with their real preferences. Future work should provide additional supports to increase ease of completing preference experiments for parents of younger children. In an upcoming international study, we have opted to provide a more thorough description of each attribute, assess understanding of each attribute, offer a detailed glossary of terms, and emphasize the availability of patient organization and research team contacts in the event of questions.

The preferences of professionals for emerging drugs have been assessed, and it is noteworthy that professionals had preferences similar to caregivers. Though only nine patients participated, patients completing this survey had preferences that were statistically unique from caregivers and professionals. Caregivers and professionals were more willing to accept possible risk in exchange for drug benefit during the DCE compared with patients. This finding is consistent with the personality evaluation wherein fewer patients identified as risk taking (33%) compared with caregivers (41%) and professionals (55%). Further research should continue to consider whether differences in these personality characteristics explain differences in benefit–risk trade-offs, and should assess preferences in a larger sample of adults.

We employed an attribute detailing 'chance of benefit' to address uncertainty. Uncertainty of outcomes in a clinical setting was found to be associated with poorer health outcomes, higher stress, and increased risk for depression [45, 46]. Therefore, we used 'chance of benefit' as a risk attribute. The participants were willing to accept uncertainty and regarded 'failure rate' as a more severe attribute than added risk of 'fracture,' but as less severe than added risk of 'kidney damage.' Our study results demonstrate that caregivers and patients are willing to accept uncertainty in treatment effects when undergoing a DBMD treatment [47, 48] if faced with the potential for a benefit to muscle function. Data regarding treatment uncertainty is important and timely given recent approval of the first Duchenne-specific treatment in the US, which was labeled as having a clinical benefit that "has not been established" [49]. Additional research should explore the ethical, legal, and social implications of patient-focused drug development in rare disorders, including how to most effectively integrate and weigh patient-preference data in the regulatory process.

We communicated risk using natural numbers, percentages, and pictographs (risk grids). Pictographs have been shown to increase the level of comprehension and decrease the influence of anecdotal reasoning compared with incremental risk demonstrated by numeric texts [50–53]. The majority of respondents experienced no difficulties in answering the tasks, though responses to open-ended feedback questions within the survey suggested that interpreting the risk grids increased the amount of time needed to complete the survey. While this is not an undesirable outcome in terms of preference assessment, it does increase respondent burden.

FDA guidance for industry regarding DBMD highlights the value of collaborating with medical professionals and industry groups in order to develop patient-focused drug treatments [6]. By including professionals, this work is consistent with the guidance. Our pragmatic approach of using the same instrument for all stakeholders required that the experiment be relevant to people with diverse experiences with DBMD, necessitating the use of a judgement-based (rather than choice-based) elicitation question. While choice-based questions are relevant for patients and caregivers who make decisions regarding drug treatments, and would consequently be approached with appropriate considerations of the risk and benefit of treatments, choice-based questions regarding treatments are neither realistic nor applicable to professionals who do not make treatment decisions in real life. As the decision was judgement rather than choice-based, the current experiment did not include an option for participants to opt-out. Omitting an opt-out allows researchers to better understand trade-offs between benefits and risks, and is common practice in regulatory benefit–risk analyses [35]. Further studies could consider how inferences might vary in the presence of an opt-out choice.

The current study has several limitations. Standard limitations of stated-preference approaches, including the hypothetical nature of questions, have been previously described and apply to the current research [19]. Recruitment through a conference organized by a patient advocacy group may limit the population to motivated participants with means and resources to travel to conferences, increasing risk of selection bias. As 93% of the respondents came from the US, the sample lacked diversity and international appeal. Although recruiting 161 respondents to the current study is a robust sample for a rare disease community, only nine patients participated, limiting the statistical power of the

results. Caution should be taken in interpreting the differences between patients and other respondents because of this sample size. In light of this limitation, results presented in this study are not intended to make policy-relevant claims. Although reaching the under-represented population and increasing overall sample diversity remains a challenge for future studies, we were able to determine that patients *can* complete advanced DCEs.

This study took a practical, rather than theoretical, approach to design and reporting. We acknowledge that the lack of theory could be considered by some as a study limitation. This research team deliberately decided to pursue a pragmatic and community-centered approach in lieu of an economic-based theoretical approach. Such an approach is consistent with changing social and political landscapes that favor patient voice and disease community collaboration over strict adherence to academic theory.

The acceptability items utilized in this research have not been formally validated, nor do we know what percent of acceptability is a 'sweet spot' for creating DCEs that are simultaneously nuanced and comprehensible. While the 75% threshold imposed in this work aligns with prior research [38], studies should further explore whether this threshold is appropriate.

We observed parent dyads of a single family completing only one survey per family based on the verbal feedback received by the research staff. The influence of parent dyads resulted in an incomplete representation of the caregivers and a decreased sample size. The suggestion for every caregiver in the family to complete the survey should be explained in the introduction section of prospective surveys to generate a greater response rate. Further studies to address the limitations could produce compelling evidence to drive the drug approval process.

5 Conclusions

We provide substantive evidence that complex discrete choice experiments are accepted by the DBMD community to evaluate emerging treatments. Using a pragmatic and community-engaged data collection approach wherein the same questionnaire is administered to multiple respondent groups, participants valued potential benefits to muscle function in a clinical trial context given treatment risks and uncertainty. This study also demonstrates the strength of these methods in presenting policy-relevant metrics such as maximum acceptable risk and in exploring how these metrics can be used to examine preference heterogeneity in a way that is accessible to community members. Building upon this promising application of DCE, future research should continue to explore the preferences of patients, caregivers, and professionals within the US and internationally.

Data availability statement The datasets generated during this study are not publicly available. Data requests should be forwarded to Ryan Fischer.

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Compliance with Ethical Standards

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Conflict of interest Ryan Fischer is an employee of Parent Project Muscular Dystrophy. John Bridges and Norah Crossnohere have received grants and support from Parent Project Muscular Dystrophy. Holly Peay has received consulting fees from Pfizer and Parent Project Muscular Dystrophy. Jui-Hua Tsai and Ellen Janssen have no conflicts of interest to declare.

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