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

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4

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

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LEADING ARTICLE

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

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Abstract

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

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

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

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

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

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

1 Introduction

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

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

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

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

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

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

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

2 Methods

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

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

2.1 Experimental Design

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

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

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

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

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

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

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

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

2.2 Statistical Analysis

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

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

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

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

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

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

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

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

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

3 Results

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

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

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

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

SE standard error

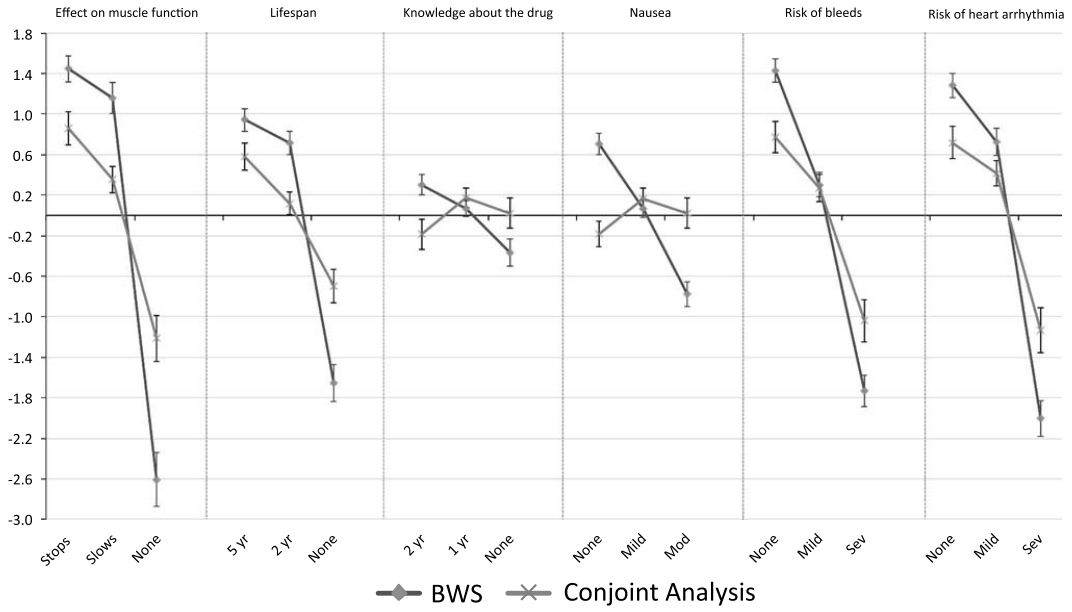

Fig. 2 Comparison of parameter estimates based on best-worst scaling and conjoint analysis. *BWS* best-worst scaling

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

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

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

4 Discussion

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

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

Table 3 Comparison of conditional attribute importance

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

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

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

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

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

Table 4 Comparative policy analysis

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

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

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

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

5 Conclusions

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

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

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

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