PATIENT-CENTERED BENEFIT–RISK ASSESSMENT IN DUCHENNE MUSCULAR DYSTROPHY

ILENE L. HOLLIN, PhD, MPH,[1] HOLLY L. PEAY, PhD,[2,3] SUSAN D. APKON, MD,[4] and JOHN F.P. BRIDGES, PhD[1]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
[2]RTI International, Research Triangle Park, North Carolina, USA
[3]Parent Project Muscular Dystrophy, Hackensack, New Jersey, USA
[4]Department of Rehabilitation Medicine, Seattle Children's Hospital and University of Washington, Seattle, Washington, USA

Accepted 17 September 2016

ABSTRACT: *Introduction:* This study quantified caregiver and patient preferences for a therapeutic agent with demonstrated pulmonary benefits for Duchenne muscular dystrophy (DMD). Caregiver and patient differences were also explored. *Methods:* A best–worst scaling survey (BWS) was administered to caregivers and patients. Across 9 profiles, respondents selected the best and worst attributes. Utility scores were estimated using mixed logistic regression. *Results:* Respondents indicated greatest preference for therapies that maintain their current level of cough strength for 10 years or for 2 years. Preference scores for risks were low: 50% chance of diarrhea and 4 additional blood draws per year. *Conclusion:* There is 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.

Muscle Nerve **000**:000–000, 2016

Regulatory decision-makers often lack reliable information to make data-driven, patient-centered benefit–risk (PCBR) assessments. In an effort to rectify this, Congress mandated that regulatory decision-makers incorporate the patients' perspective into benefit–risk assessment.[1,2] PCBR assessment is an increasingly favored approach for doing this in a vigorous way.[3] Historically, the U.S. 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 assessments because of their ability to provide information about factors that patients and families will trade off 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 it 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 and sponsors regarding what, how, and when patient preference data may be considered during the review process.[6,7] In 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 these data for preference-sensitive decisions in which there is significant uncertainty and/or when patients' views may differ considerably from those of researchers and clinicians.[7]

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, thus 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 (PPMD), an advocacy organization focused on finding a cure for Duchenne and Becker muscular dystrophy (DBMD), developed draft guidance for industry that calls for incorporating patient preferences.[9,10] The FDA followed with its own draft guidance for industry in developing drugs for DBMD that considers patient and caregiver benefit–risk tolerance and preference heterogeneity in regulatory decisions.[11] Duchenne muscular dystrophy (DMD) is an inherited neuromuscular disorder of pediatric onset. It causes progressive muscle weakness, loss of ambulation, and pulmonary decline. Affected

Abbreviations: BWS, best–worst scaling; BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; DBMD, Duchenne and Becker muscular dystrophy; FDA, U.S. Food and Drug Administration; PCBR, patient-centered benefit–risk; PPMD, Parent Project Muscular Dystrophy

Key words: best–worst scaling; Duchenne/Becker muscular dystrophy; patient-centered benefit–risk assessment; patient preferences; quality of life; regulatory review

Disclosure: H.P. was an employee of the Parent Project Muscular Dystrophy at the time of this research.

This study was supported by the Parent Project Muscular Dystrophy (PPMD, to I.H. and J.B.). PPMD received funding for this project from Santhera Pharmaceuticals. This work was also supported by a Patient-Centered Outcomes Research Institute (PCORI) Methods Program award (ME-1303-5946 to J.B.) and by the Johns Hopkins–FDA Center for Excellence in Regulatory Science and Innovation (1U01FD004977-01 to J.B.).

Correspondence to: I.L. Hollin, National Pharmaceutical Council and University of Southern California Schaeffer Center for Health Policy & Economics, 1717 Pennsylvania Avenue NW, Suite 800, Washington, DC 20006; e-mail: ihollin@npcnow.org

Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.25411

individuals have a shortened lifespan with respiratory failure, pneumonia, and cardiac involvement as the leading causes of death.[12–16] Becker muscular dystrophy (BMD) has a similar phenotype to DMD, but it has milder manifestations and slower progression.[17] At the time of the study there were no FDA-approved therapies for DBMD; the gold standard for treatment relies on off-label use of corticosteroids, which has been shown to have some benefits with regard to attenuating muscle loss and improving cardiopulmonary function.[18–20] Side effects of long-term steroid use include obesity, behavioral problems, osteoporosis, delayed puberty, gastroesophageal reflux, cataracts, and risk of infections.[21]

Despite significant progress in developing a framework and proposing processes for incorporating patient preferences in regulatory decision-making, it is still a nascent field. There are 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 used previously to quantify patient preferences for hypothetical therapeutic options that would slow the progression of muscle weakness.[22] The study reported here, however, describes a preference study developed in direct response to guidance for sponsors. The objective of this study was to quantify patient and caregiver preferences for a therapeutic agent for DBMD that has 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 second decade.[12–16] We hypothesized that caregivers and patients would be willing to trade moderate risk for pulmonary benefits. A secondary objective was to explore caregiver and patient preferences. We expected that caregivers and patients may have different preferences.

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 into 3 committees (leadership, stakeholder, and review committee) and provided feedback at various timepoints to allow for an iterative design approach. The review committee also participated in cognitive interviews. This pilot-testing technique allowed us to analyze whether participants understood the questions as intended by the researcher.[23,24] Additional details about the community-engaged approach and the model for survey development have been published elsewhere.[24]

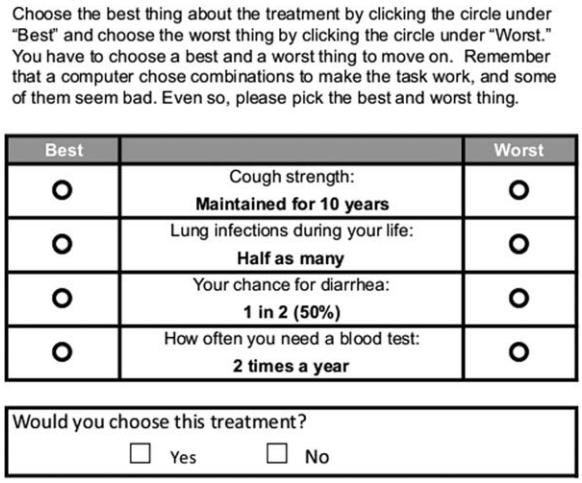

FIGURE 1. Sample choice task for BWS case 2 (profile) experiment and follow-up intention to use question

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 4 stated-preference exercises, although only the results of the best–worst scaling (BWS) case 2 (profile case) experiment and a follow-up simple discrete choice task are reported here. BWS is a stated-preference method that has been developed recently and continues to grow in popularity among healthcare applications.[25–34] In BWS case 2, respondents evaluate 1 treatment profile at a time and provide 2 data points per profile (best and worst).[35] Across 9 choice tasks, respondents selected the best and worst attributes from among 4 attributes at 3 varying levels, 1 of which was a reference level of no benefit or no risk. Benefits did not represent disease reversal, or even reversal of impact on the lungs, 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 of 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, 2 additional blood draws per year, or

4 additional blood draws per year). See Figure 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 to be useful for patient preference research intended to inform regulatory decision-making, because the interpretation and application of the data combination assists one to understand risk tolerance, meaningful benefits, and intention to use specific therapies.[36]

A 3×4 main effects orthogonal, experimental design was used such that the attribute levels presented for each attribute across tasks were balanced and uncorrelated. This design is accessible because it can be identified from the SAS database of orthogonal arrays. It was also chosen for its statistical efficiency because it uses the minimum number of treatment profiles to ensure uncorrelated attributes.[34,37–39]

Recruitment. Respondents were recruited between June 18, 2015 and July 30, 2015 through multiple sources targeted at qualifying individuals. Recruitment began at the PPMD annual conference and was followed by targeted e-mails directed to DuchenneConnect registry participants. Respondents were also recruited through a grass-roots, parent-led outreach initiative of PPMD.

Eligibility criteria included living in the United States and being either the caregiver of someone living with DBMD or a patient with the same condition. Caregivers had to be at least age 18 years old, and their affected child was required to be at least 10 years old. This cut-off was chosen to maximize participation while minimizing potential negative psychological implications of a survey about pulmonary decline for parents of very young children. Stakeholder engagement demonstrated that parents of a young child may not have fully considered the impact of their child's pulmonary decline given that it does not manifest until later in the disease course and leads to emotional upset.[24] The minimum age for patient respondents was 14 years. The protocol for this study was approved by the institutional review board (IRB) of Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (IRB # 00006299). All participants provided informed consent electronically. Teen respondents participated with a guardian's permission.

Table 1. Demographics of caregiver respondents and their affected child

	Caregivers ($n = 82$)	
	Frequency	Percent
About child affected with DBMD		
Age		
10–13 years	36	44%
14–17 years	26	32%
18–25 years	14	17%
25^{+} years	6	7%
Diagnosis		
Duchenne	72	88%
Becker	8	10%
Intermediate	2	2%
Ambulation status		
Ambulatory	34	41%
Non-ambulatory	48	59%
Steroid use		
Current or previously	68	83%
Never	13	16%
Insurance type		
Private	38	46%
Public	16	20%
Both	28	34%
About caregiver respondents		
Age		
30–45 years	36	44%
45^{+} years	46	56%
Race		
White	72	88%
Hispanic	6	7%
Native	4	5%
Black/African American	4	5%
Asian	1	1%
Other	1	1%
Household income		
<$50,000	13	16%
$50,001–$75,000	18	22%
$75,001–$100,000	24	29%
>$100,000	16	20%
Region		
Northeast	15	18%
Midwest	15	18%
South	29	35%
West	23	28%
Marital status		
Single	6	7%
Married/long-term relationship	59	72%
Divorced/separated/widowed	16	20%
Relationship to affected individual		
Biological mother	63	77%
Biological father	13	16%
Adoptive mother	5	6%
Grandmother guardian	1	1%
Highest level of education		
High school graduate	34	41%
College graduate	29	35%
Graduate/professional degree	18	22%

Rows within a category may sum to less than 100% due to missing data. Missing data counts by variable as follows: steroid use (n = 1); race (n = 1); income (n = 11); marital status (n = 1); and education (n = 1). Race categories are not mutually exclusive.

Analysis. Fisher exact tests were used to test for differences in relevant characteristics of affected individuals with DBMD across caregiver and patient respondents. Differences in 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.[40] 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 was anchored at zero. The magnitudes of the coefficients were compared to calculate maximum acceptable risk and minimum acceptable benefit. Probabilities of intention to use therapy were estimated by calculating the percentages of respondents who selected that they would use the treatment. We calculated relative attribute importance using best-minus-worst scores (number of times an attribute/level combination was chosen as best minus the number of times it was chosen as worst) by calculating the difference between the highest and lowest best-minus-worst scores for each attribute and dividing it by the sum of all differences. We conducted exploratory analyses looking at results stratified by respondent type (caregivers or patients). All analyses were conducted using STATA version 14 (StataCorp, College Station, Texas).

RESULTS

Descriptive Statistics. A total of 133 respondents completed the BWS case 2 experiment comprised of 61.7% caregivers ($n = 82$) and 38.3% DBMD patients ($n = 51$). Table 1 provides a complete list of caregiver respondent characteristics, and Table 2 provides patient respondent demographics. Caregiver respondents were primarily biological mothers (77%). Other caregiver types included biological fathers (16%), adoptive mothers (6%), and a grandmother acting as a guardian (1%). The majority of caregivers were married or in long-term relationships (72%). 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%) and living in higher income households; 71% of caregivers and 50% of patients were living in households earning more than $50,000 per year.

Table 2. Demographics of patient respondents

	Patients ($n = 51$)	
	Frequency	Percent
Age		
14–17 years	13	25%
18–25 years	16	31%
25^+ years	22	43%
Diagnosis		
Duchenne	42	82%
Becker	9	18%
Intermediate	0	0%
Ambulation status		
Ambulatory	14	27%
Non-ambulatory	37	73%
Steroid use		
Current or previously	35	69%
Never	16	31%
Insurance type		
Private	20	39%
Public	8	16%
Both	23	45%
Race		
White	47	92%
Hispanic	4	8%
Native	1	2%
Black or African American	2	4%
Asian	2	4%
Other	1	2%
Household income		
<$50,000	17	33%
$50,001–$75,000	8	16%
$75,001–$100,000	7	14%
>$100,000	10	20%
Region		
Northeast	10	20%
Midwest	8	16%
South	21	41%
West	12	24%
Marital status		
Single	29	57%
Married/long-term relationship	9	18%
Divorced/separated/widowed	0	0%

Rows within a category may sum to less than 100% due to missing data. Missing data counts by variable: race (n = 1); income (n = 9); and marital status (n = 13). Race categories are not mutually exclusive.

Most affected individuals had a diagnosis of DMD. Although this was lower among adult respondents (82%) compared with caregiver respondents (88%), this was not a statistically significant difference. The majority of affected individuals had current or past history of steroid use. Caregivers reported that 83% of their affected children had current or past history of steroid use,

Table 3. Mixed logit results for caregiver and patient preferences for benefits and risks

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

Coefficient (mean) from mixed logistic regression. 95% CI, 95% confidence interval around the coefficient; SD, standard deviation of the mean.

**Difference in means test between 2 groups.*

and 69% of patients reported current or past history of steroid use. The majority of affected individuals were either privately insured (caregivers: 46%; patients: 39%) or privately insured and receiving public insurance (caregivers: 34%; patients: 45%). 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 was expected, given the eligibility criteria for participation. There was also a wider range for the age of affected individuals among patient respondents, which is consistent with the larger proportion of respondents in that group with BMD, which is associated with longer lifespan.

Utility Scores. The results of mixed logit analyses for the stratified groups are shown in Table 3. Respondents demonstrated the greatest preference for a therapeutic agent that maintains their current level of cough strength for 10 years [caregiver score: 1.697, 95% confidence interval (CI) 1.44–1.95; patient score: 1.446, 95% CI 1.19–1.74] and for 2 years (caregiver score: 0.716, 95% CI 0.49 to 0.94; patient score: 0.746, 95% CI 0.44–1.05). Although respondents preferred half as many lung infections (caregiver score: 1.118, 95% CI 0.90–1.34; patient score: 0.907, 95% CI 0.65–1.16) over very few lung infections (caregiver score: 0.790, 95% CI 0.52–1.06; patient score: 0.870, 95% CI 0.59–1.15), the overlap in the CIs between the 2 levels demonstrated no significant difference in preferences.

Respondents had the lowest preference for a therapeutic agent with no benefit to cough strength (caregiver score: –2.413, 95% CI –2.70 to –2.13; patient score: –2.212, 95% CI –2.54 to –1.88), followed by an agent with no benefit to lung infections (caregiver score: –1.908, 95% CI –2.21 to –1.61; patient score: –1.777, 95% CI –2.08 to –1.47). These were preferred less than even a 50% risk of diarrhea (caregiver score: –0.884, 95% CI –1.08 to –0.68; patient score: –0.561, 95% CI –0.81 to –0.31).

As shown in Table 3, the differences in preference scores were not statistically significantly

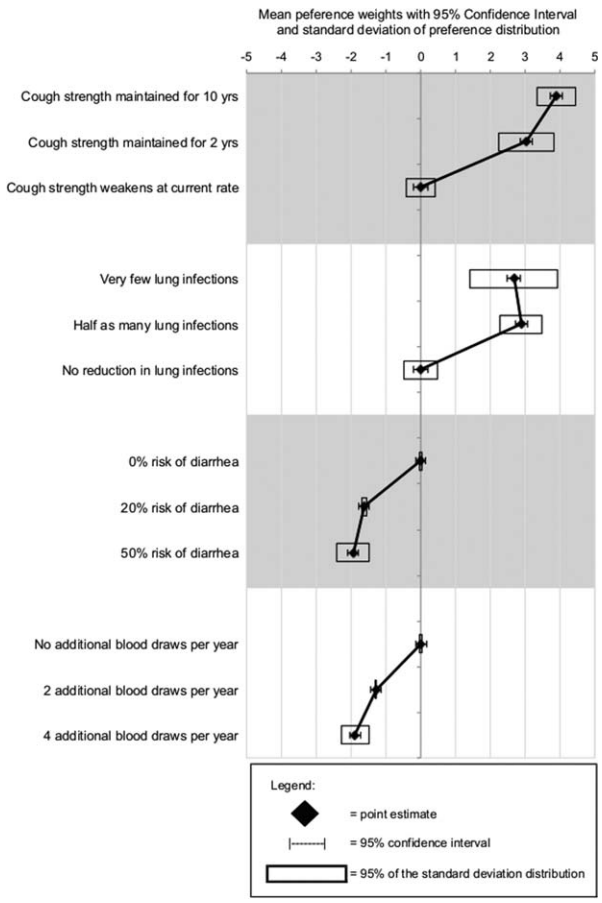

FIGURE 2. Mixed logit results for aggregate preferences for benefits and risks

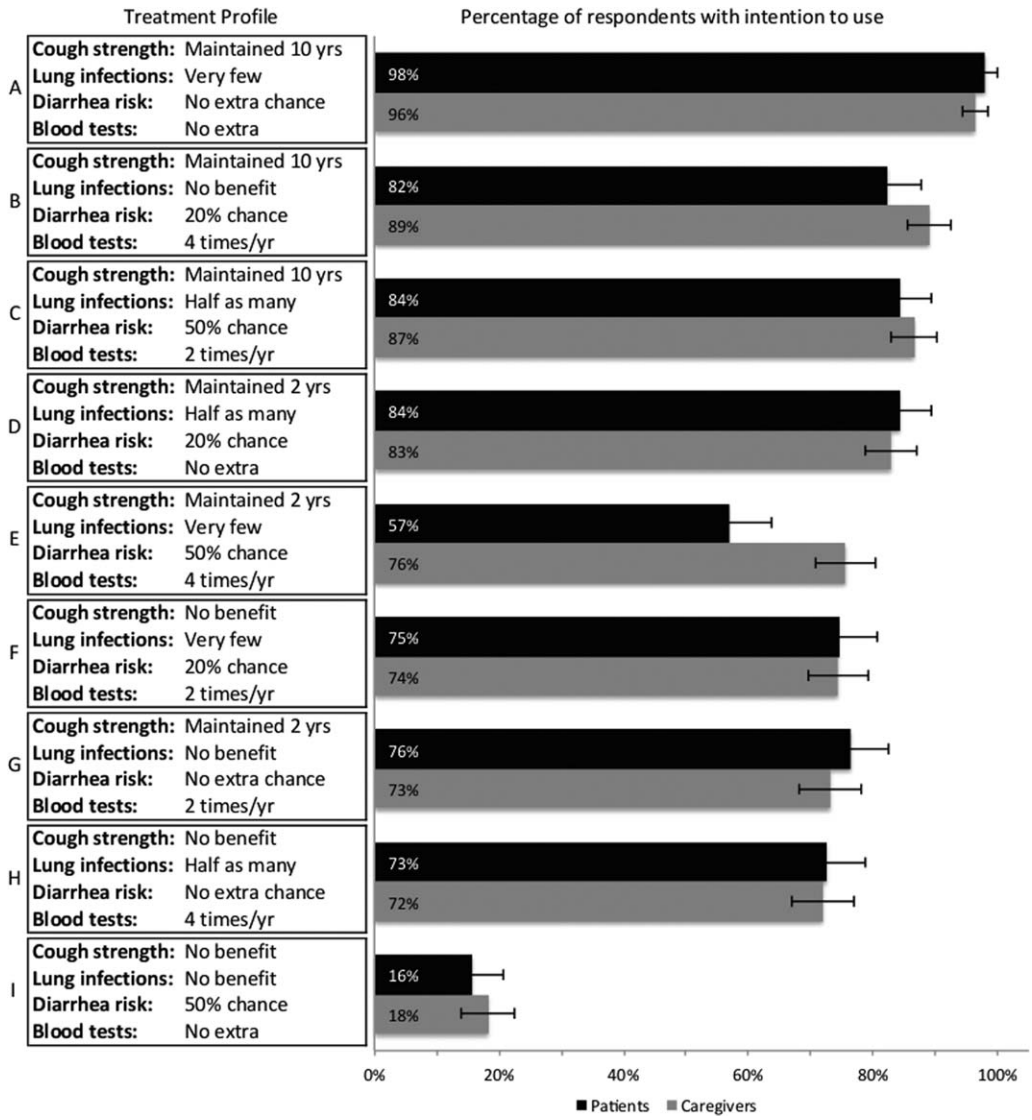

FIGURE 3. Probability representing intention to use treatment profile by respondent type and corresponding treatment profiles

different across caregiver and patient groups. Furthermore, the standard deviations of the preference scores were not statistically significant for 75% of the attribute/level combinations. $P < 0.05$ 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 2 groups. Therefore, to understand attribute importance, minimal acceptable benefit, and maximum acceptable risk, pooled results are shown in Figure 2. The magnitude of the coefficient for cough strength maintained for 2 years (3.03) is greater than the combined magnitude of the coefficients for 20% risk of diarrhea (–1.63) and 2 additional blood draws (–1.28), indicating that these risks fell within maximum acceptable risk for an additional 2 years of maintaining cough strength (Fig. 2).

Analysis of relative attribute importance reveals that respondents were most concerned with a treatment's ability to address benefits compared with its risks. Results are similar across both groups, with 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 3, for 8 of 9 profiles, there was a >65% probability that respondents intended to use the treatment. For 4 treatment profiles, there was a >80% probability of use. All of these profiles had a benefit of

maintaining cough strength for at least 2 years, and 3 of 4 had a moderate benefit for lung infections. For most treatment profiles, there were no significant differences between caregivers and patients, with 1 exception. Treatment profile E had a 57% probability of take-up among patients and a 76% probability of take-up among caregivers.

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 with 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 to maintain their current level of cough strength for up to 10 additional years. The maximum risk that participants were willing to accept to maintain their cough strength for 2 years was 20% risk of diarrhea and blood monitoring an additional 2 times per year.

Preference scores for "no benefit to cough strength" and "no benefit to lung function" were the lowest, which demonstrates that respondents preferred some risk over no benefit to cough strength or lung infections. This has major implications for quantifying patient and caregiver 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 whether they intended 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 Fig. 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 each other. 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 nonattendance to any single attribute, which indicates respondents differentiated between the 2 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. Based on community input, levels for this attribute were described in qualitative terms rather than presented with absolute benefit in percentages. "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 were provided with an educational portion before the choice tasks in which they were given assumptions about the attribute and level definitions. Despite this, because "very few" is not quantifiable and "half as many" is quantifiable, the ordinal nature of the levels described in the educational section 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 it 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 toward the benefits relative to the risks demonstrates a 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 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 benefit–risk trade-offs in a broader population.

A limitation of the study is that the results may be subject to sample bias. The sampling strategy is likely to be over-inclusive of a motivated pool of people who attend conferences or are active contributors to the registry and may have different preferences compared with the general DBMD population. Future work intends to elicit preferences from a nationally representative sample.

In conclusion, these results demonstrate a strong preference for therapies with a pulmonary benefit and willingness to trade off risks and burdens 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 regard to treatment outcomes. Furthermore, patient preference information can highlight potential differences in views between clinicians and patients. This is also more likely with 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 has demonstrated the capacity of community-engaged preference research to provide data about variables that are meaningful to patients and families. Furthermore, it shows the influence of FDA guidance in promoting the use of such methods to inform the drug development process.

The authors appreciate the time and commitment of all the community members who serve on the leadership, stakeholder, and review committees. We are indebted to all of the caregivers and individuals with Duchenne and Becker muscular dystrophy who participated in the survey. We also thank Caroline Hanson and Caroline Young for help in designing the instrument and programming the data collection tool.

REFERENCES

1. Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112–144, 126 Stat. 993, codified as amended at 21 U.S.C. §301 (2012).
2. Thaul S. Prescription Drug User Fee Act (PDUFA): 2012 Reauthorization as PDUFA V. 2013. Congressional Research Service Report for Congress R42366. https://www.fas.org/sgp/crs/misc/R42366.pdf.
3. van Til JA, Ijzerman MJ. Why should regulators consider using patient preferences in benefit-risk assessment? Pharmacoeconomics 2014;32:1–4.
4. U.S. Food and Drug Administration. Guidance for industry and Food and Drug Administration staff: factors to consider when making benefit-risk determinations in medical device premarket approval and *de novo* classifications. 2012. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationsandGuidance/GuidanceDocuments/UCM51704.pdf/.
5. Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, *et al.* Incorporating patient-preference evidence into regulatory decision making. Surg Endosc 2015;29:2984–2993.
6. Hunter NL, O'Callaghan KM, Califf RM. Engaging patients across the spectrum of medical product development: view from the US Food and Drug Administration. JAMA 2015;314:2499–2500.
7. U.S. Food and Drug Administration. Patient preference information—submission, review in premarket approval applications, humanitarian device exemption applications, and *de novo* requests, and inclusion in device labeling: draft guidance for industry, Food and Drug Administration staff, and other stakeholders. 2015. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationsandGuidance/GuidanceDocuments/UCM446680.pdf/.
8. Medical Device Innovation Consortium (MDIC). Patient centered benefit-risk project report: a framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology. Minneapolis, MN: MDIC; 2015.
9. Furlong P, Bridges JFP, Charnas L, Fallon JR, Fischer R, Flanigan KM, *et al.* How a patient advocacy group developed the first proposed draft guidance document for industry for submission to the U.S. Food and Drug Administration. Orphanet J Rare Dis 2015;10.
10. Parent Project Muscular Dystrophy (PPMD). Guidance for industry Duchenne muscular dystrophy: developing drugs for treatment over the spectrum of disease. 2014. https://static-content.springer.com/esm/art%3A10.1186%2Fs13023-015-0281-2/MediaObjects/13023_2015_281_MOESM3_ESM.pdf.
11. U.S. Food and Drug Administration. Duchenne muscular dystrophy and related dystrophinopathies: developing drugs for treatment guidance for industry. 2015. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationsandGuidance/GuidanceDocuments/UCM450229.pdf/.
12. Inkley SR, Oldenburg FC, Vignos, PJ. Pulmonary function in Duchenne muscular dystrophy related to stage of disease. Am J Med 1974;56:297–306.
13. Rideau Y, Jankowski LW, Grellet J. Respiratory function in the muscular dystrophies. Muscle Nerve 1981;4:155–164.
14. McDonald CM, Abresch RT, Carter GT, Fowler WM, Johnson ER, Kilmer DD, *et al.* Profiles of neuromuscular diseases. Duchenne muscular dystrophy. Am J Phys Med Rehabil 1995;74(suppl):S70–92.
15. Tangsrud S, Petersen IL, Lodrup Carlsen KC. Lung function in children with Duchenne's muscular dystrophy. Respir Med 2001;95:898–903.
16. Kohler M, Clarenbach CF, Boni L, Brack T, Russi EW, Bloch KE. Quality of life, physical disability, and respiratory impairment in Duchenne muscular dystrophy. Am J Respir Crit Care Med 2005;172:1032–1036.
17. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010;9:77–93.
18. Biggar W, Harris V, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscul Disord 2006;16:249–255.
19. Angelini C. The role of corticosteroids in muscular dystrophy: a critical appraisal. Muscle Nerve 2007;36:424–435.?
20. Bushby K, Muntoni F, Urtizberea A, Hughes R, Griggs R. Report on the 124th ENMC International Workshop. Treatment of Duchenne muscular dystrophy; defining the gold standards of management in the use of corticosteroids 2-4 April 2004, Naarden, The Netherlands. Neuromuscul Disord 2004;14:526–534.
21. Ricotti V, Ridout DA, Scott E, Quinlivan R, Robb SA, Manzur AY, *et al.* Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry 2013;84:698–705.
22. Peay HL, Hollin I, Fischer R, Bridges JF. A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. Clin Ther 2014;36:624–637.
23. Collins D. Pretesting survey instruments: an overview of cognitive methods. Qual Life Res 2003;12:229238.
24. Hollin I, Young C, Hanson C, Bridges J, Peay H. Developing a patient-centered benefit-risk survey: a community-engaged approach. Value Health 2016;15:751–757.
25. Louviere JJ, Flynn TN. Using best-worst scaling choice experiments to measure public perceptions and preferences for healthcare reform in Australia. Patient 2010;3:275–283.
26. Molassiotis A, Emsley R, Ashcroft D, Caress A, Ellis J, Wagland R. Applying best–worst scaling methodology to establish delivery preferences of a symptom supportive care intervention in patients with lung cancer. Lung Cancer 2012;77:199–204.
27. Marti J. A best–worst scaling survey of adolescents' level of concern for health and non-health consequences of smoking. Soc Sci Med 2012;75:87–97.
28. Flynn TN, Louviere JJ, Peters TJ, Coast J. Estimating preferences for a dermatology consultation using best-worst scaling: comparison of various methods of analysis. BMC Med Res Methodol 2008;8:76.
29. Swancutt DR, Greenfield SM, Wilson S. Women's colposcopy experience and preferences: a mixed methods study. BMC Womens Health 2008;8:2.
30. Coast J, Salisbury C, De Berker D, Noble A, Horrocks S, Peters TJ, *et al.* Preferences for aspects of a dermatology consultation. Br J Dermatol 2006;155:387–392.
31. Gallego G, Bridges JFP, Flynn T, Blauvelt BM, Niessen LW. Using best-worst scaling in horizon scanning for hepatocellular carcinoma technologies. Int J Technol Assess Health Care 2012;28:339–346.
32. Finn A, Louviere JJ. Determining the appropriate response to evidence of public concern: the case of food safety. J Public Policy Mark 1992:12–25.
33. Marley AA, Louviere JJ. Some probabilistic models of best, worst, and best–worst choices. J Math Psychol 2005;49:464–480.
34. Bridges JF, Kinter ET, Kidane L, Heinzen RR, McCormick C. Things are looking up since we started listening to patients. Patient 2008;1:273–282.

35. Flynn TN. Valuing citizen and patient preferences in health: recent developments in three types of best-worst scaling. Expert Rev Pharmacoecon Outcomes Res 2010;10:259–267.
36. Hollin IL, Peay HL, Bridges JF. Caregiver preferences for emerging duchenne muscular dystrophy treatments: a comparison of best-worst scaling and conjoint analysis. Patient 2015;8:19–27.
37. Kinter ET, Prior TJ, Carswell CI, Bridges JF. A comparison of two experimental design approaches in applying conjoint analysis in patient-centered outcomes research. Patient 2012;5:279–294.
38. Johnson FR, Lancsar E, Marshall D, Kilambi V, Mühlbacher A, Regier DA, *et al.* Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force. Value Health 2013; 16:3–13.
39. Kuhfeld W. Orthogonal arrays [TS-723]. Technical note. Cary, NC: SAS; 2010. http://www.support.sas.com/techsup/technote/t3723.pdf/.
40. Louviere JJ, Islam T. A comparison of importance weights and willingness-to-pay measures derived from choice-based conjoint, constant sum scales and best–worst scaling. J Bus Res 2008;61:903–911.