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Development and psychometric analysis of the Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT)

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Abstract

The objective of this study was to describe the development and initial psychometric analysis of the UK English version of the Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT), a patient-reported outcome (PRO) scale designed to measure functional ability in patients with Duchenne muscular dystrophy (DMD). Item selection was made by neuromuscular specialists and a Rasch analysis was performed to understand the psychometric properties of the DMDSAT. Instrument scores were also linked to cost of illness and health-related quality of life data. The administered version, completed by 186 UK patient–caregivers pairs, included eight items in four domains: Arm function, Mobility, Transfers, and Ventilation status. These items together successfully operationalized functional ability in DMD, with excellent targeting and reliability (Person Separation Index: 0.95; Cronbach's α : 0.93), stable item locations, and good fit to the Rasch model (mean person/item fit residual: -0.21 – -0.44 , SD: 0.32/1.28). Estimated item difficulty was in excellent agreement with clinical opinion (Spearman's ρ : 0.95) and instrument scores mapped well onto health economic outcomes. We show that the DMDSAT is a PRO instrument fit for purpose to measure functional ability in ambulant and non-ambulant patients with DMD. Rasch analysis augments clinical expertise in the development of robust rating scales.

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1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disease with an incidence of about one in 3800–6300 live male births [1]. The predominant feature of DMD is progressive muscle weakening, which at onset presents as delayed motor milestones (e.g., running and jumping). As the disease progresses, patients' functional ability diminish, resulting in loss of independent ambulation and serious orthopaedic, cardiac, and respiratory complications [2,3]. Mean

age at death is 25 years [4], but some patients now survive to experience their fourth decade of life.

To help track and facilitate management and monitoring of the progression of DMD, four categories of disease (early/late ambulatory/non-ambulatory) were proposed by the DMD Care Considerations Working Group in the DMD care guidelines [2,3]. However, given the considerable heterogeneity in rate of progression and associated complications across patients with DMD, these categories lack granularity both with respect to applications of therapies in clinical practice, as well as endpoints in trials. Moreover, existing clinical measures in DMD only apply to ambulatory patients (e.g., the North Star Ambulatory Assessment, NSAA [5,6]) or non-ambulatory patients (e.g., the Performance of the Upper Limb, PUL [7]) or lack sensitivity and reliability in DMD (e.g., the Vignos scale [8] and Brooks scale [9]) and are thus not fit to map precisely stages of disease trajectory.

EL, AM, and ME, and HL and KB, respectively, contributed equally.

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The purpose of this study was to describe the development and initial psychometric analysis of the UK English version of the DMD Functional Ability Self-Assessment Tool (DMDSAT), a patient-reported outcome (PRO) scale designed to measure and categorize functional ability across the entire lifetime of disease progression in patients with DMD. Our aim was to create a clinically and personally relevant tool that could be easily completed by the patient or a caregiver (e.g., a parent) without the assistance of a healthcare professional. To inform health policy evaluations of DMD interventions, we also sought to map the instrument scores to health economic outcomes, including previously published estimates of costs of illness and patient health-related quality of life (HRQL) [10,11].

2. Materials and methods

2.1. Instrument development

We declared the underlying latent trait to be operationalized by the DMDSAT as “functional ability” (i.e., ability which encompasses physical and respiratory functioning and which describes highly relevant progression and staging of the disease and identifies specific requirements for interventions [2,3]), encompassing the full range within the DMD progression sequence (i.e., from the early ambulatory to late non-ambulatory disease stage). Given that our objective was to create a simple tool that easily could be completed by patients and/or their caregivers, we sought to capture the latent trait through manifestations in common activities of daily living (e.g., getting on and off the floor, on and off the toilet, and climbing up and down stairs). In addition, to allow further discrimination of functional ability, we also wanted to include items relating to manifestations of the lower and upper extremities, respectively, as well as ventilation status.

Given these aims, an initial set of items (questions) and levels (response categories) was generated by a group of neuromuscular specialists and specialist neuromuscular physiotherapists with extensive experience in the medical management of DMD. The list of items and their specification was also informed by a non-systematic literature review of existing measures. To capture the patient-perspective, items within the draft set were discussed with and tested on patients and caregivers in a clinical setting (as part of patients’ routine clinical follow-up) to assure understandability (e.g., that the items and levels made sense and were easily understood) and completeness (e.g., that all essential levels were represented, relevant, and appropriately formulated in terms of hierarchy). We also conducted a pilot study, comprising five randomly chosen patients, with follow-up questions to test the database platform and further assure understandability and completeness. Minor modifications were made following additional review of items and levels by the DMD specialists.

2.2. Participants and procedures

The instrument was developed as part of a multinational, cross-sectional study for which details and results have been previously reported [10–12]. In summary, DMD patients from Germany, Italy, the UK, and the US were identified through the

Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases (TREAT-NMD) network [13]. To be eligible, patients were required to fulfil the following criteria: (i) Male, (ii) DMD diagnosis, and (iii) Age ≥ 5 years. Eligible patients and one of their caregivers (e.g., a parent) completed a study questionnaire comprising the DMDSAT administered online. As the aim of this report was to validate the UK version of the DMDSAT, only UK replies were included in the psychometric analyses.

All participants provided informed consent. Study ethical approval was granted from Ludwig-Maximilians-Universität München (Germany), Comitato Etico IRCCS E. Medea – Associazione La Nostra Famiglia (Italy), North East Research Ethics Service, NHS (UK), and the Western Institutional Review Board (US). Approval was also obtained from the TREAT-NMD Global Databases Oversight Committee.

2.3. Rasch analysis

Rasch analysis was used to assess the psychometric properties of the new instrument. Rasch analysis is the formal testing of a scale against a mathematical model developed by the Danish mathematician Georg Rasch [14], and is considered to be superior to traditional psychometric methods [15]. In brief, there are three main components to the theory of Rasch measurement. First, a person’s response to an item is governed by two factors only: (i) person ability (e.g., level of disease severity) and (ii) item difficulty (i.e., the level of severity expressed by the item). The probability that a person will affirm an item is a function of the distance between person ability and item difficulty. The second component is a probabilistic form of the Guttman response pattern, which states that if a person affirms a task then there is a high probability that easier tasks will also be affirmed (e.g., that a person who is able to walk longer distances would also be expected to be able to walk short distances). The third component to the theory of Rasch measurement is Rasch’s criterion of invariance, which ensures that results for scales are sample independent and results for samples are scale independent, and is described elsewhere [15]. The Rasch analysis output consists of an interval-level scale or metric (logit scale) to which both respondents and items are located following the three listed analysis components. Given good fit of the data to the Rasch model, the interval scale allows for the meaningful interpretation of mean total scores, as well as change in total scores. Rasch analysis also provides a unified approach to test several measurement issues which further helps ensure that the scale yields meaningful, interpretable results.

2.4. Statistical analysis

We tested the psychometric properties of the DMDSAT by analysing item and person fit to the Rasch partial credit model (misfit defined as $|\text{fit residual}| > 2.5$ or item chi-square Bonferroni-adjusted p-value < 0.006), item dependency (i.e., if a reply to one item predicts the reply to another item), ordering of item response category thresholds (i.e., that respondents are able to differentiate between response categories), reliability (Person Separation Index [PSI], indicating the possibility of

the scale to differentiate between respondents at different levels of functional ability, and Cronbach's α), targeting (i.e., the match of the different ability levels estimated through the Rasch model with the ability levels observed in our sample), and item stability (i.e., differential item functioning, investigated by glucocorticoid treatment, Bonferroni-adjusted p-value <0.002) [15]. In addition, all instrument items were also analysed for clinical validity and interpretability. To this end, the item thresholds were ranked in terms of difficulty by DMD experts (n = 7), and this order was subsequently compared with the Rasch analysis ordering of items in terms of difficulty using Spearman's ρ .

We mapped the DMDSAT total scores to our previously published estimates of costs [10] and patient HRQL (utilities) [11] through regression analysis. Specifically, generalized linear models with mean per-patient annual costs and mean patient and caregiver utility as dependent variables were fitted to the data. DMDSAT total score was the main explanatory variable. The models were also adjusted for income class, and common mental and behavioural disorders, as well as a dummy variable indicating additional household member with DMD, to control for confounding effects.

The psychometric analysis was conducted in RUMM2030 (RUMM Laboratory, Perth, Australia). All additional analyses were conducted in Stata 12 (StataCorp LP, College Station, TX, US).

3. Results

A total of 186 UK patients with DMD completed the DMDSAT according to instructions together with one of their caregivers (186 patient-caregiver pairs). Patients had a mean age of 14 years (range 5–43) and a median age of 12 years (IQR 8–17). Approximately 45% of all patients were wheelchair dependent and 19% required ventilation support (day and/or night). Additional details of the study sample have been previously published [10–12].

3.1. Psychometric properties of the DMDSAT

The administered version of the DMDSAT included a total of eight items in four domains: *Arm function*, *Mobility*, *Transfers*, and *Ventilation status* (Fig. 1). Two items, *Arm function* and *Mobility*, initially displayed disordered thresholds, indicating that participants had difficulty discriminating

between response categories given their functional ability. The response categories for these items were consequently revised by the DMD experts based on clinical observation and rescored as shown in Fig. 2. Category probability curves displaying thresholds for the *Arm function* item before and after rescored are shown in Fig. 3. A threshold map of all items is available as supplemental material (online). Upon re-scoring, the total DMDSAT score ranged from 0 (low functional ability) to 23 (high functional ability).

Table 1 presents the fit of the items to the Rasch model, ordered by level of difficulty in terms of functional ability (lower value indicates low difficulty, and vice versa). No items displayed model misfit in terms of estimated residuals, but *Get on and off the toilet* had a significant chi-square probability (due to marginal under-discrimination). In accordance with the ranking of item thresholds by seven international DMD specialists, the most difficult item was *Go up and down stairs*, followed by *Get on and off the floor*. Overall agreement between model and expert rankings was excellent (Spearman's $\rho = 0.95$). Mean item dependency was low (−0.007), and only two items (*Get in and out of bed* and *Get on and off the toilet*) displayed positive correlation >0.30.

Fit of individual responses to the Rasch model was good (mean fit residual: −0.205, SD: 0.318). Patients were evenly distributed across elicited ability levels, floor and ceiling effects were minimal (2% and 6%, respectively), and the estimated scale encompassed ability levels both lower and greater than those observed in the sample (Fig. 4). The PSI was estimated at 0.95 and Cronbach's α at 0.93, indicating very good reliability. The model chi-square statistic was estimated at 45, $p < 0.001$, suggesting that the items did not form a unidimensional scale. By investigating residual principal component loadings, we found that we would obtain unidimensionality by excluding the *Arm function* item (chi-square statistic 18, $p = 0.208$). Analysis of scale stability showed that there was no significant uniform or non-uniform differential item functioning by glucocorticoid treatment (all $p > 0.045$ and $p > 0.201$, respectively).

3.2. Association between DMDSAT, total cost of illness, and patient quality of life

The mean change in per-patient annual cost of illness associated with a one-point increase in DMDSAT total score was estimated at 5.3% (95% CI: 4.6%–5.9%, $p < 0.001$) when

Table 1
Individual item fit to the Rasch model.

Item	Location (item difficulty) ^a	SE	Fit residual (observed-expected)	χ^2	χ^2 probability
Ventilatory status	−5.56	0.25	−0.20	0.34	0.846
Arm function	−3.03	0.13	2.13	9.46	0.009
Get in and out of bed	0.26	0.20	−0.88	6.81	0.033
Get in and out of a chair	0.59	0.20	−1.43	6.74	0.034
Get on and off the toilet	0.71	0.20	−0.11	13.62	0.001
Mobility	1.21	0.13	−2.31	1.59	0.451
Get on and off the floor	2.28	0.18	−0.35	4.39	0.111
Go up and down stairs	3.54	0.18	−0.32	2.00	0.367

Note: Mean item fit residual = −0.435 (SD = 1.28).

^a A low number represents low difficulty, and vice versa.

The DMD Functional Ability Self-Assessment Tool (DMDSAT)

The questions below describe levels of activity for arm function, mobility, transfers, and need for ventilatory support. The activities are intended to be in order of difficulty and we would like you to **tick the box that best applies to your current level of function**.

Arm function		Select one	
Can put an item such as book onto a shelf above shoulder height		<input type="radio"/>	
Can lift at least one arm above head		<input type="radio"/>	
Can lift at least one arm to shoulder height		<input type="radio"/>	
Can eat a meal without any help		<input type="radio"/>	
Needs help to cut up food but can feed and drink independently		<input type="radio"/>	
Needs help to drink or feed self		<input type="radio"/>	
Can pick objects up e.g. pen/money		<input type="radio"/>	
Can move fingers e.g. press on mobile or other electronic device		<input type="radio"/>	
Cannot move fingers		<input type="radio"/>	

Mobility		Select one	
Walks independently long distances outdoors (more than 1 km)		<input type="radio"/>	
Walks independently medium distances outdoors (less than 1 km)		<input type="radio"/>	
Walks independently outdoors for short distances, e.g. to car		<input type="radio"/>	
Walks outdoors with help from a person		<input type="radio"/>	
Walks indoors independently but requires wheelchair for outdoors		<input type="radio"/>	
Walks indoors with help from a person requires wheelchair outdoors		<input type="radio"/>	
Uses wheelchair indoors and outdoors		<input type="radio"/>	
Uses wheelchair but unable in some situations e.g. cold weather		<input type="radio"/>	
Unable to control wheelchair without help		<input type="radio"/>	

Transfers	Can do independently	Can do with help	Needs to be lifted or hoisted or cannot
Get on and off the floor	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Get in and out of a chair	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Get in and out of bed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Get on and off the toilet	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Go up and down stairs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Ventilatory support	Not ventilated	Ventilated at night	Ventilated during day and night
Ventilatory status	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Fig. 1. The DMD Functional Ability Self-Assessment Tool (DMDSAT).

adjusting for household income class, common mental and behavioural disorders, and additional household member with DMD. The corresponding mean loss in patient utility was 9.5% (95% CI: 9.0%–10.1%, $p < 0.001$). Spearman's ρ between predicted and observed total cost of illness and patient utility was estimated at 0.61 and 0.85 ($p < 0.001$), respectively.

Additional cost and utility analysis results are available as supplemental material (online).

4. Discussion

In recent years, the importance of PROs from rating scales in medical science has increased considerably [15]. The US Food

Arm function	Original score	Re-score
Can put an item such as book onto a shelf above shoulder height	8	6
Can lift at least one arm above head	7	
Can lift at least one arm to shoulder height	6	5
Can eat a meal without any help	5	
Needs help to cut up food but can feed and drink independently	4	4
Needs help to drink or feed self	3	3
Can pick objects up e.g. pen/money	2	2
Can move fingers e.g. press on mobile or other electronic device	1	1
Cannot move fingers	0	0

Mobility	Original score	Re-score
Walks independently long distances outdoors (more than 1 km)	8	5
Walks independently medium distances outdoors (less than 1 km)	7	4
Walks independently outdoors for short distances, e.g. to car	6	
Walks outdoors with help from a person	5	3
Walks indoors independently but requires wheelchair for outdoors	4	
Walks indoors with help from a person requires wheelchair outdoors	3	2
Uses wheelchair indoors and outdoors	2	1
Uses wheelchair but unable in some situations e.g. cold weather	1	
Unable to control wheelchair without help	0	0

Fig. 2. DMDSAT arm function and mobility item scoring structure. Note: Transfer/Ventilatory support items were scored 0 = Can do independently/Not ventilated; 1 = Can do with help/Ventilated at night; and 2 = Needs to be lifted or hoisted or cannot/Ventilated during day and night.

and Drug Administration, for example, now require evidence in terms of PROs in all submissions, and endpoints in clinical trials are to a growing extent defined in terms of outcomes from rating scales. Given their prevalence in clinical practice and research, and their implication on health care and health policy, it is thus critical to ensure that rating scales used are “fit for purpose” [16].

The objective of this study was to describe the development and Rasch analysis of the DMDSAT, a new self-assessment rating scale measuring functional ability in patients with DMD. During instrument development, we identified four domains which we envisioned would capture this latent trait as manifested in DMD: *Arm function*, *Mobility*, *Transfers*, and *Ventilation status*. *Transfers* comprised five items relating to activities of daily living, i.e., “Get on and off the floor”, “Get in and out of a chair”, “Get in and out of bed”, “Get on and off the toilet”, and “Go up and down stairs”. Overall, our analysis showed that these items together successfully operationalized functional ability in DMD, with excellent targeting and reliability, stable item locations irrespective of glucocorticoid treatment, and good overall fit to the Rasch model.

Initially, our Rasch analysis of the DMDSAT revealed that two items, *Arm function* and *Mobility*, exhibited disordered thresholds, and these were subsequently rescored for purpose of analysis. Specifically, for *Arm function*, we collapsed three categories, namely, “Can lift at least one arm above head”, “Can lift at least one arm to shoulder height”, and “Can eat a meal without any help”. The original scoring identified these as distinct objectives that change over time in a given order;

however, the analysis identified a lack of progression in difficulty indicating that e.g., a boy with DMD may find that he can eat a meal without any help but still find bringing an arm above his head as difficult. Thus, given the lack of distinction between thresholds, we decided to rescore these as indicated in Fig. 2. For the *Mobility* item, we collapsed three separate pairs of items, namely, (i) “Uses wheelchair but unable in some situations e.g. cold weather” and “Unable to control wheelchair without help”, (ii) “Walks indoors independently but requires wheelchair for outdoors” and “Walks indoors with help from a person requires wheelchair outdoors”, and (iii) “Walks independently outdoors for short distances e.g. to car” and “Walks outdoors with help from a person”. The lack of distinction between levels in set (i) may be explained by the fact that both describe a boy in need of assistance for steering his wheelchair and thus an individual who no longer is independent in terms of mobility. For sets (ii) and (iii), although from a clinical viewpoint they would be expected to mark different abilities, the lack of differentiation between response categories may reflect variability in patient preference, or possibilities to be assisted, rather than functional ability (e.g., walk a short distance with support from someone vs. using a wheelchair without any help).

Upon revising the scoring algorithm for *Arm function* and *Mobility*, the DMDSAT exhibited excellent targeting, with good coverage of both patient abilities (top chart area, Fig. 4) and item difficulties (bottom chart area, Fig. 4) along the continuum. Less than 2% (3 of 186) of patients had the minimum score and 6% (11 of 186) the maximum score, well

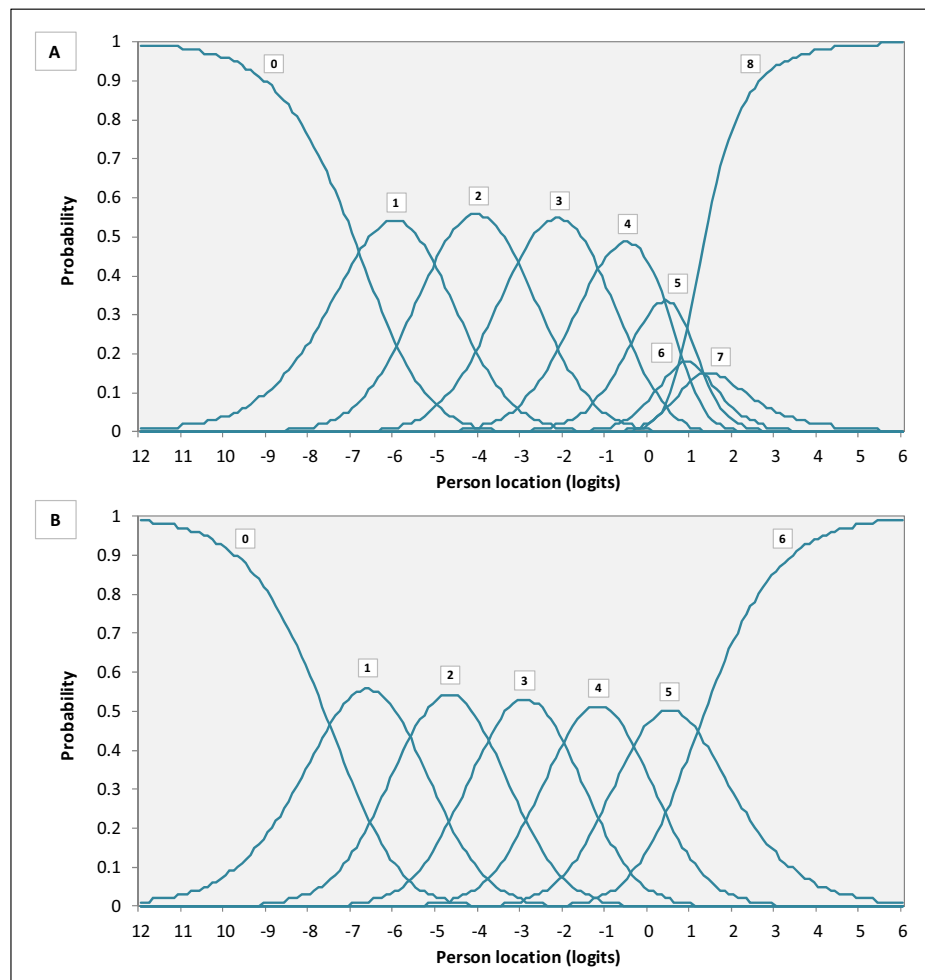


Fig. 3. Category probability curves for arm function, before (A) and after (B) rescoring. Note: As shown in panel A, respondents had difficulty discriminating between response categories 5, 6, and 7 (5 = “Can lift at least one arm above head”, 6 = “Can lift at least one arm to shoulder height”, and 7 = “Can eat a meal without any help”). For purpose of analysis, these categories were collapsed into a single category (category 5 in panel B).

below proposed upper limits for floor and ceiling effects of 15% and 20% [14]. The Rasch analysis also showed that the DMDSAT had very good reliability. Specifically, the PSI was estimated at 0.95, which means that our construct can differentiate between five groups of responders, and Cronbach’s α at 0.93, markedly higher than the recommended thresholds of 0.70 and 0.80 [15]. We also noted excellent agreement between the Rasch model and expert rankings of item thresholds in terms of difficulty, supporting the clinical validity and interpretation of the DMDSAT total scores.

In the analysis, we identified a positive dependency between two items, namely, *Get in and out of bed* and *Get on and off the toilet*. The correlation may be explained by similarity in the physical ability required to perform the tasks. However, upon removing one of the items, the PSI changed only by 0.007 (<0.8%), indicating that this dependency did not artificially inflate reliability. From a clinical point of view, given the different muscles involved in e.g., getting out of bed and off the toilet, and also because the tasks encompass different spheres of life (independence inside vs. outside of the home), including both items was deemed justified.

Although our analysis demonstrated that fit of all items to the Rasch model was good, we noted that unidimensionality (which is a requirement for interval measures) could be improved by removing the *Arm function* item. This finding suggests that *Arm function* also measures a latent trait other than functional ability, which is certainly possible given the variation in disease manifestations both between and within patients and stages of DMD progression. In addition, using modern technology, a patient not able to move his fingers may in fact be able to control a wheelchair without any help, complicating the interpretation of the hierarchical relationship of item thresholds in terms of functional ability. Moreover, for some patients, reduced functional ability of the upper extremities may not be apparent until they are dependent on wheelchairs for mobility, but may already be present whilst they are ambulant. For these reasons, and given our objective to capture total function rather than disjointed function of arms and legs separately, we decided to retain *Arm function* in the scale, also as it contributed substantially to differentiating between respondent abilities, in particular among the less able boys. However, given that the other tests displayed good fit to

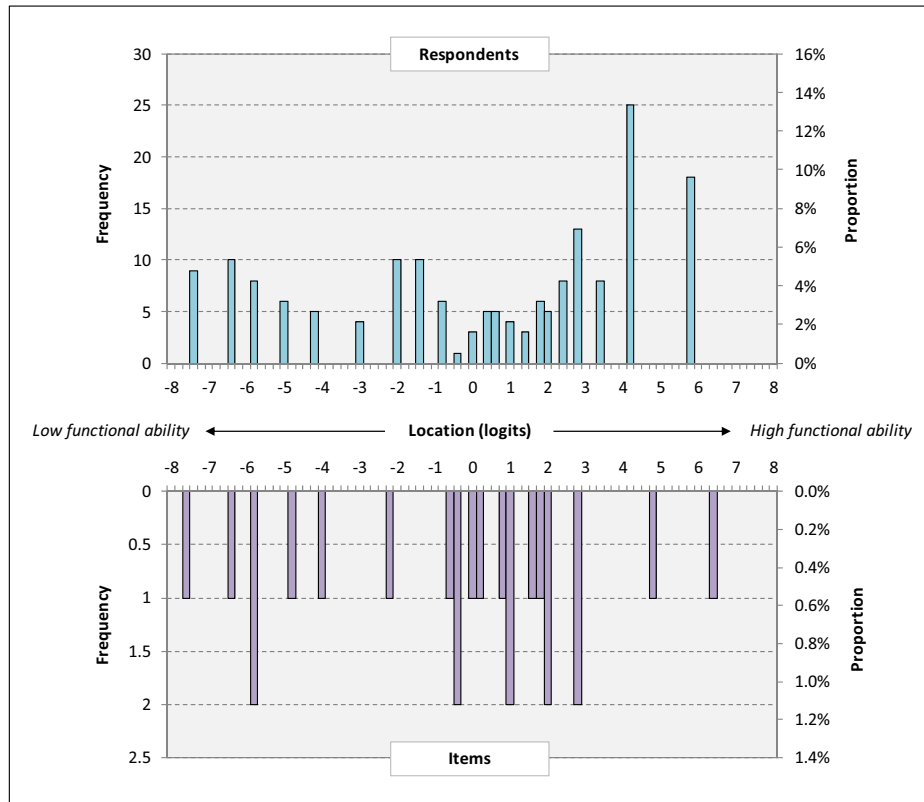


Fig. 4. Distribution of respondents and items on the logit continuum. Note: The top chart area shows the location of the DMD patients on the interval logit scale representing the level of functional ability (a low number represents low functional ability, and vice versa). The bottom chart area shows the location of the DMDSAT items on the same logit scale (a low number represents low item difficulty, and vice versa).

the Rasch model, the impact of this issue in terms of interpreting total DMDSAT scores would be expected to be minor. Additional analysis of the relationship between arm and leg functions in DMD is needed to further validate clinical and patient rating scales.

We estimated the mean change in annual cost of illness per one-point increase in DMDSAT total score at 5.3%, and a mean loss in patient utility of 9.5%. These estimates should be helpful to inform cost-effectiveness analysis of DMD interventions, in particular model frameworks where progression and health states are defined in terms of DMDSAT scores, which will allow for more differentiated assessments as compared to e.g., the early/late ambulatory/non-ambulatory classes. Moreover, given that the DMDSAT was developed as a complement to existing scales in an attempt to add granularity not only to trial assessments but also to assignment of care standards to different disease stages, the scale should have utility in many different settings, including clinical practice, research, and health policy.

The strengths of our study include the comparably large sample of DMD patients, who usually are very difficult to identify due to the rarity of the disease, encompassing an extensive range of disease severity (i.e., levels of functional ability), as well as the comprehensive Rasch analysis (deemed superior to traditional psychometric analysis [15]). The main limitation of our study concerns generalizability, as our patient

sample was recruited through the TREAT-NMD network and it is not known to what extent this population is representative of all DMD patients in the UK (although differences in terms of clinical manifestations would be expected to be very minor). It should also be noted that future research is needed to further validate the DMDSAT and assess properties such as responsiveness, test–retest reliability, and minimally important difference thresholds.

In summary, we show that the DMDSAT is a PRO instrument fit for purpose to measure functional ability in ambulant and non-ambulant patients with DMD. It complements existing clinical rating scales and map well onto health economic outcomes in this population. Rasch analysis augments clinical expertise in the development of robust rating scales.

Contributions

Mr. Landfeldt, Dr. Lindgren, and Mr. Bell designed the study with input from Dr. Lochmüller and Dr. Bushby. Dr. Mayhew and Dr. Eagle led the development of instrument item identification and selection. Mr. Landfeldt co-ordinated ethics approval processes and managed the collection of data. Mr. Landfeldt designed, implemented, and executed the statistical analysis. Mr. Landfeldt, Dr. Mayhew, and Dr. Eagle led the interpretation of findings with input from the other authors. Mr.

Landfeldt drafted the manuscript. All authors reviewed the manuscript and approved the decision to submit for publication.

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Appendix: Supplementary material

Supplementary data to this article can be found online at [doi:10.1016/j.nmd.2015.09.012](https://doi.org/10.1016/j.nmd.2015.09.012).

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