Published in final edited form as:

Muscle Nerve. 2014 June ; 49(6): 906–914. doi:10.1002/mus.24097.

The Myotonic Dystrophy Health Index: Initial Evaluation of a New Outcome Measure

Chad Heatwole, M.D., M.S.-C.I.¹, Rita Bode, Ph.D.², Nicholas Johnson, M.D.¹, Jeanne Dekdebrun, M.S.¹, Nuran Dilek, M.S.¹, Mark Heatwole, B.S., M.B.A.³, James E. Hilbert, M.S.¹, Elizabeth Luebke, M.S.¹, William Martens, B.A.¹, Michael P. McDermott, Ph.D.^{1,4}, Nan Rothrock, Ph.D.⁵, Charles Thornton, M.D.¹, Barbara G. Vickrey, M.D., M.P.H.^{6,7}, David Victorson, Ph.D.⁵, and Richard Moxley III, M.D.¹

¹The University of Rochester Medical Center, Department of Neurology, Rochester, NY

²Psychometric Consultant, Chicago, IL

³The United States Government Accountability Office, Retired

⁴The University of Rochester Medical Center, Department of Biostatistics and Computational Biology, Rochester, NY

⁵Northwestern University Feinberg School of Medicine, Chicago, IL

⁶David Geffen School of Medicine, UCLA Medical Center, Los Angeles, CA

⁷Greater Los Angeles VA HealthCare System, Los Angeles, CA

Abstract

Introduction—In preparation for clinical trials we examine the validity, reliability, and patient understanding of the Myotonic Dystrophy Health Index (MDHI).

Methods—Initially we partnered with 278 myotonic dystrophy type-1 (DM1) patients and identified the most relevant questions for the MDHI. Next, we used factor analysis, patient interviews, and test-retest reliability assessments to refine and evaluate the instrument. Lastly, we determined the capability of the MDHI to differentiate between known groups of DM1 participants.

Results—Questions in the final MDHI represent 17 areas of DM1 health. The internal consistency was acceptable in all subscales. The MDHI had a high test-retest reliability (ICC=0.95) and differentiated between DM1 patient groups with different disease severities.

Conclusion—Initial evaluation of the MDHI provides evidence that it is valid and reliable as an outcome measure for assessing patient-reported health. These results suggest that important aspects of DM1 health may be effectively measured using the MDHI.

Keywords

Myotonic Dystrophy Type-1; Patient-Reported Outcome Measure; Therapeutic Trial; Quality of Life; Patient-Relevant; Muscle Disease

Introduction

Myotonic dystrophy type-1 (DM1) is a dominantly inherited, multi-system disorder caused by an unstable CTG repeat expansion on chromosome 19.^{1–3} DM1 affects many organ systems causing a wide array of clinical symptoms. The heterogeneity of DM1 creates a challenge in developing a patient-reported outcome measure that is valid, reliable, responsive, and capable of monitoring the variety of symptoms that are most meaningful to the DM1 population.⁴

In a previous cross-sectional study of 278 DM1 patients (the PRISM-1 study) we identified a wide range of symptoms that affect the DM1 population with variable levels of importance. We then created a model of disease burden for this population.⁵ We used these data in creating the Myotonic Dystrophy Health Index (MDHI), a disease-specific, patient-reported outcome measure to estimate the overall disease burden and the impact of key symptomatic themes in DM1 patients. The MDHI and its subscales are designed for use in clinical trials and as an instrument to support drug labeling claims as directed by the United States Food and Drug Administration (FDA).⁶ Below we detail how the MDHI was created and how we assess its content validity, construct validity, test-retest reliability, sensitivity in differentiating known cohorts of DM1 patients, and acceptability to patients.

Materials and Methods

Eligibility Criteria

Participants were 21 years of age or older and had a diagnosis of DM1 by genetic and/or clinical criteria.^{7, 8} None of the participants carried the diagnosis of congenital or childhood onset myotonic dystrophy. DM1 participants were recruited through the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members (<http://www.urmc.rochester.edu/nihregistry/>)⁹, from Muscular Dystrophy Association Clinics, and from those that had participated in a DM1 disease progression study. Three different DM1 patient groups were utilized. The baseline characteristics and research role of all three groups are provided in Table 1 with additional details regarding the study participants provided in Supplementary Table 1. All research activities were approved by the Institutional Review Board at the University of Rochester.

The Myotonic Dystrophy Health Index Creation and Testing

Question Selection and Content Validity—In previous work we used structured interviews to identify the major symptoms experienced by individuals with DM1, and then we formatted questions to quantify each symptom's frequency and life impact in a cohort of 278 individuals (the PRISM-1 study).⁵ In the current study we prioritized the symptoms (identified in PRISM-1) by their relative importance to DM1 patients. Questions

representing prioritized symptoms were selected for additional evaluation and potential use in the MDHI. Questions with a population impact score⁵ (range 0 to 4) below 0.45 were excluded from the MDHI. Other PRISM-1 questions were excluded if our research team had consensus that the question was: 1) redundant; 2) potentially offensive to future respondents; 3) not amenable to therapeutic intervention; 4) not applicable to a broader DM1 population; 5) of vague meaning; or 6) above a grade-school reading level.

Exploratory Factor Analysis and Internal Consistency of Subscales—

We grouped questions based on content into subscales representing key DM1 themes. Questions designed to measure a single hypothesized theme were grouped and placed into one of two forms which were administered to our sample of 278 DM1 patients (Group 1). We subsequently performed exploratory factor analysis on the questions in each subscale to determine if they were measuring a similar concept. To perform this task we used Mplus software (<http://www.statmodel.com>), polychoric correlations that are appropriate for categorical data, an unweighted least squares estimation procedure, and quartimin rotation of the factor loadings.¹⁰ Response data obtained from Group 1 were used for this analysis.⁵ Eigenvalues were examined to determine the number of factors within each subscale, with factors having eigenvalues >1 being retained. Questions with factor loadings ≥ 0.30 were determined to load on a particular factor (i.e., the questions represented a single theme). Questions loading primarily on secondary factors (with smaller loadings) and those with factor coefficients <0.30 on the primary factor were considered for transfer, depending on content, to a more appropriate subscale. For subscales in which a single factor was identified, we used Cronbach's alpha to evaluate the internal consistency of the questions (i.e., the degree that the subscale questions were measuring the same construct).¹¹

Patient Assessment with Cognitive Interviews—Following factor analysis, we constructed the first version of the MDHI and conducted semi-structured interviews with ten DM1 participants (Group 2; Table 1) to determine the comprehension, ease of use, response processes, and recall strategies (time frame of responses) of the instrument.¹² Participants who provided consent were mailed a copy of the MDHI to complete, and were interviewed after completing the MDHI.

Through cognitive interviewing¹³, participants described what each question meant to them (comprehension probe), discussed how sure they were of their answers (confidence probe), discussed the perceived time frame of the responses, remarked on the wording of each question and theme, commented on the response choices, reported the time needed to complete the instrument, identified any problematic formatting issues, discussed the clarity of the instructions, commented on the scoring strategy, and identified any symptoms that were not adequately addressed. All participant responses were audio recorded, transcribed, de-identified, and analyzed using a three-investigator consensus approach.¹² Specific questions were reworded or removed if poorly understood or if there was an inconsistent perception of the question by interviewed participants.

Test-Retest Reliability—We assessed the test-retest reliability of the MDHI in a cohort of 22 subjects with DM1 (Group 3; Table 1). The time between the two surveys ranged from 5 to 31 days. A five day minimum was selected to minimize patient recall of prior

questionnaire responses. We choose a 31 day maximum given the relatively slow progression of disease in DM1 and the low likelihood that patient symptoms would significantly change (due to progression of disease) during this period.¹⁴ The reliability of the scores across administrations for the total instrument, each subscale, and each question was assessed. Intraclass correlation coefficients (ICCs) were used to quantify the reliability of the instrument.¹⁵ A two-way mixed-effects model with random subject effects and a fixed effect of time or administration (first, second) was utilized. We identified questions with poor reliability (ICC <0.70) for potential deletion from the final instrument. Upon completion of the final MDHI, we performed a final exploratory factor analysis on all subscales to take into account any questions that had been dropped throughout the MDHI's development.

Scaling and Scoring of the MDHI—The weight of each question in the MDHI was set to represent the relative importance of the specific symptom in Group 1. Each question was weighted in proportion to its population impact score as determined in PRISM-1.⁵ Any questions added after PRISM-1 were assigned the average weight of the associated subscale questions representing the same theme. The weighted sum of responses was transformed to a 0–100 scale by expressing it as a percentage of the maximum possible value with a score of 100 representing the most severe disease burden and a score of zero representing no disease impact. We refer to this weighted overall score as the MDHI total score. A similar algorithm was developed to compute individual scores (range: 0–100) for each subscale.

Known Groups Validity and Final Factor Analysis—The average MDHI total score and subscale scores were determined for multiple predefined subgroups believed to differ in terms of disease severity. DM1 respondents were categorized by employment status (employed, not employed), CTG repeat length (<300, ≥300), highest level of education obtained (no college degree, college or advanced degree), duration of symptoms (<20 years, ≥20 years), age (21–47, ≥47), and gender. Data from the PRISM-1 study (Group 1) were utilized for this analysis.⁵ For groups involving age, duration of symptoms, and CTG repeat length, cutoff points were selected to roughly divide the sample in half. Questions added after the PRISM-1 study were treated as missing data and assigned a value equal to the average of associated questions in their subscale. Values for re-worded questions were based on responses given to the original question. Because each PRISM-1 participant was originally randomly assigned to complete only one form (approximately one-half of the questions), a total score could not be computed at the participant level. The mean and standard error of the total score could be estimated at the group level; however, by combining the information from both halves of the instrument, taking into account the weighting of the individual questions and the number of people who responded to each question. Group comparisons of the mean MDHI total scores were performed using z-tests. Since subscale scores were available at the participant level, group comparisons of the mean subscale scores were performed using t-tests.

RESULTS

Question selection

We started with 235 original symptom questions. Of these, we retained 114 questions for the final version of the MDHI. Questions that would potentially respond to psychological, environmental, psycho-social, physical, or pharmacological interventions were left in the instrument. Figure 1 provides an overview of the total process used to develop and select questions for the MDHI.

Exploratory Factor Analysis and Internal Consistency of Subscales

Groups of questions representing 15 themes (subscales) were analyzed using response data from Group 1. Within subscales, 12 questions were placed in a different subscale based on low item-subscale correlation or to improve statistical fit.

Factor analysis led to the addition of four themes and the removal of one theme. The question “breathing difficulties” was selected as a symptomatic theme due to its importance to patients and its lack of statistical fit within other subscales. The theme “problems with your vision, hearing, or smell” was replaced with a “vision” theme and a “hearing” theme. The “sense of smell” aspect of the original theme was not needed as all questions related to smell had been previously excluded due to low population impact scores.

At the completion of this research, an exploratory factor analysis was performed on all subscales in the final MDHI. The final subscales representing thematic question groups had high internal consistencies with an average Cronbach’s alpha of 0.89 (range 0.76 to 0.98). Table 2 provides details regarding the internal consistency of each subscale. Supplementary Table 2 provides additional measurement characteristics of the MDHI subscales.

Patient Assessment with Qualitative Interviews

Ten DM1 patients of varying clinical severity (Group 2) completed the MDHI and provided specific recommendations to optimize the format, wording, ease of use, scoring, comprehension, and clarity of instruction of the instrument. Based on the suggestions of these participants, we revised the wording of six questions to improve clarity (e.g. “cramping” was changed to “muscle cramping” and “memory deficits” was changed to “memory problems”). We excluded one question because interviewees had an inconsistent understanding of the phrase “visual spatial difficulties”.

Participants stated that the instructions were clear, that they were comfortable with the questions, and that they had no trouble completing the survey. Participants demonstrated understanding of the item responses and reported that there were adequate response options to describe their symptoms. Participants were able to identify the theme of each subscale based on its questions, and they did not view any of the questions in the MDHI as offensive. The average time reported to complete the MDHI was 19 minutes (range: 10–30 minutes).

Test-Retest Reliability

Twenty-two participants (Group 3) completed the MDHI twice over a one-month period with an average interval of 10.2 days (range 5 to 31 days) between testing. No participant achieved a maximum score on the MDHI. All questions but three had an ICC greater than the standard threshold of 0.70.¹⁶ We removed one question from the final instrument because of a low ICC (“foot pain” (0.641)). Similarly, we removed one question/theme “side effects from medications” due to a low ICC (0.594). The third question, related to “excessive sleep requirements” (0.690), was retained in the final instrument due to its high prevalence (87.1%) and relative importance to the DM1 population.⁵ At the end of this stage, the final version of the MDHI was established. The MDHI total score had an ICC of 0.95. Table 2 lists ICC values for each of the final MDHI subscales. The test-retest reliability data is shown graphically in Figure 2.

Known groups and validity

The MDHI total score and selected subscale scores reliably differentiated between cohorts of DM1 patients suspected to have a higher burden of disease. Higher mean MDHI total scores were found in DM1 groups (group 1) with no employment, less education, longer CTG repeat lengths, and longer duration of symptoms (Table 3, Table 4, Figure 3). The greatest difference in mean MDHI total score was observed between employed and unemployed DM1 participants (25.0 vs. 41.5). There was no difference in mean MDHI total score between male and female participants; however, older DM1 participants had greater mean MDHI total scores ($p < 0.01$). Total and subscale scores based on gender and age are provided in Supplementary Table 3.

DISCUSSION

The Myotonic Dystrophy Health Index (MDHI) is a novel disease-specific, multifaceted patient-reported outcome measure for the most common adult muscular dystrophy. Designed for use in clinical trials, the MDHI estimates disease burden and is comprised of 17 subscales that measure the most important symptomatic DM1 themes.

Disease-specific instruments like the MDHI have inherent advantages over generic instruments in measuring outcomes during clinical trials. Disease-specific instruments can focus on the questions that are most relevant to a select disease population while excluding those that are less relevant. Disease-specific instruments also tend to have increased precision, simpler application, better responsiveness, greater relevance, fewer ceiling effects, and heightened sensitivity in detecting clinically significant response to treatment over time.^{17–19}

The MDHI is a patient-reported outcome measure (PROM). As such, it has the potential to identify subtle relevant clinical changes in disease burden and contribute to the comprehensive evaluation of novel therapeutics.²⁰ Critical yet subtle clinical changes are often detected by patients prior to detection using clinician-administered measures. To this end, PROMs are recommended by the FDA to support drug labeling claims and to measure the effect of treatment on patient function and well-being.^{6, 21, 22} The reporting of PROMs

as primary or secondary outcome measures in randomized controlled trials has also recently been highlighted in an extension of the CONSORT (Consolidated Standards of Reporting Trials) guidelines.²³ Our study sought to implement the rigorous methodology recommended by the FDA to ensure both the content validity of the MDHI and its potential use for drug labeling claims following positive clinical trials.⁶ Although DM1 experts were involved in its development, the content of the MDHI was largely guided by direct patient data and input. All of the critical DM1 symptoms and themes addressed in the MDHI were validated by DM1 patients. This methodology was implemented to comply with the FDA's eight nonbinding recommendations for ensuring the content validity of a patient-reported outcome measure.⁶

The creation of the MDHI adds to several existing outcome measures available for myotonic dystrophy research. Two notable existing myotonic dystrophy specific instruments include the muscular impairment rating scale (MIRS) and the DM1-Activ (a myotonic dystrophy activity and participation scale). In contrast to the MIRS, a 5-point examiner-administered scale based primarily on strength, the MDHI measures a patient's perception of their multifactorial disease state without requiring direct administration, assessment, or observation by a clinical examiner.²⁴ In comparison to the DM1-Activ, the MDHI was designed to measure a broad spectrum of patient relevant DM1 symptoms (beyond just activity and participation). In addition, the MDHI does not appear to be significantly limited by ceiling or floor effects. This is in contrast to the DM1-Activ which was reported to have a ceiling effect in 1/12 DM1 participants, a potentially limiting factor for use in therapeutic studies.²⁵

The MDHI total score consistently demonstrated its ability to differentiate between clinically distinct subgroups of DM1 patients. Although there is not a universally accepted mechanism for defining disease severity in DM1, average MDHI total scores consistently detected a greater burden of disease in DM1 subgroups suspected to have more severe disease. The differences in MDHI total scores between patients grouped by CTG repeat length, education level (more severely affected patients are hypothesized to have a restricted ability to advance in school), duration of symptoms, and employment status provides a clinical reference for interpreting changes in MDHI scores during future clinical or therapeutic trials. Longitudinal studies are needed to determine the MDHI's potential for detecting patient relevant changes in response to treatment and further evaluate the performance of the scale. Additional studies are also needed to compare the responsiveness of the MDHI against those of traditional clinician administered functional measures and other patient-reported outcome instruments.

One limitation of our research relates to the low prevalence of DM1 in the general population. As would be expected during the development of any instrument for a rare disease, the use of methods based on item response theory to address dimensionality was limited. Another limitation relates to the iterative processes required to create a PROM. Our known groups validity testing relied on data from a large cross-sectional study performed near the beginning of instrument development. Although the wording of most questions remained unchanged during MDHI development, six questions were reworded based on patient input. Despite these slight wording modifications, the initial responses by 278

participants to the originally worded questions were used for analysis. We will need additional studies using a separate sample of DM1 participants to verify the psychometric properties of the MDHI given these minor wording changes.

The MDHI was designed to meet a critical need for clinical trial readiness in DM1.^{26, 27} In preparation for upcoming clinical trials of novel DM1 therapeutic agents, it is important to have outcome measures capable of capturing patient-relevant changes in status.⁴ The reproducibility of the MDHI is high, allowing researchers to primarily attribute MDHI score changes to aspects other than scale instability. The MDHI's high test-retest reliability improves its potential to reduce sample size requirements, a critical factor in enhancing the feasibility of clinical trials. The MDHI provides a multidimensional tool to measure a wide range of symptoms and themes directly reported by patients to be important to their lives. The presence of 17 separate subscales allows researchers the flexibility to observe clinical effects in multiple focused areas of DM1 patient health simultaneously. The diverse subscales in the MDHI can be used by DM1 researchers interested in studying symptom-specific interventions, such as anti-myotonia therapies, ambulation devices, pain treatments, antidepressants, cognitive therapies, gastrointestinal medications, or sleep modifying strategies. Alternatively, researchers may use the MDHI to help monitor a patient's perception of their combined health status throughout a therapeutic trial.

The results described in this manuscript are the necessary initial steps in the development of the MDHI. Future research will focus on the validation of the instrument by examining the responsiveness of the subscales and comparing the scores with other outcomes and scales. Our initial results suggest that the MDHI may prove useful as a clinical trial outcome measure for the myotonic dystrophy type-1 population. This instrument provides an option for researchers to measure a patient's perception of their multisystem disease in response to therapy during clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study Funding: Support for this research was provided by the National Institute of Arthritis and Musculoskeletal and Skin Disorders (1K23AR055947), the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (U54NS48843-01), the Muscular Dystrophy Association, and the Saunders Family Fund. The project described in this publication was also supported by the University of Rochester CTSA award number UL1 RR024160 from the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health.

Partial support for this research was provided by the National Institute of Arthritis and Musculoskeletal and Skin Disorders (1K23AR055947), the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (NINDS U54NS48843), the Muscular Dystrophy Association, and the Saunders Family Fund. The project described in this publication was also supported by the University of Rochester CTSA award number UL1 RR024160 from the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Additional information regarding the MDHI is available at the *Neuromuscular Institute of Quality-of-Life Studies and Outcome Measure Development* website www.QOLINSTITUTE.com and MDHI licensing opportunities can be reviewed at: www.urmc.rochester.edu/techtransfer.

Abbreviations

MDHI	The Myotonic Dystrophy Health Index
DM1	Myotonic dystrophy type-1
FDA	United States Food and Drug Administration
PRISM-1	Patient-Reported Impact of Symptoms in Myotonic Dystrophy Type-1
ICC	Intraclass correlation coefficient
PROM	Patient-Reported Outcome Measure

References

1. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell*. 1992; 68:799–808. [PubMed: 1310900]
2. Fu YH, Pizzuti A, Fenwick RG Jr, King J, Rajnarayan S, Dunne PW, et al. An unstable triplet repeat in a gene related to myotonic muscular dystrophy. *Science*. 1992; 255:1256–1258. [PubMed: 1546326]
3. Mahadevan M, Tsilfidis C, Sabourin L, Shutler G, Amemiya C, Jansen G, et al. Myotonic dystrophy mutation: an unstable CTG repeat in the 3' untranslated region of the gene. *Science*. 1992; 255:1253–1255. [PubMed: 1546325]
4. Foff EP, Mahadevan MS. Therapeutics development in myotonic dystrophy type 1. *Muscle Nerve*. 2011; 44:160–169. [PubMed: 21607985]
5. Heatwole C, Bode R, Johnson N, Quinn C, Martens W, McDermott MP, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1). *Neurology*. 2012; 79:348–357. [PubMed: 22786587]
6. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. Department of Health and Human Services Food and Drug Administration. Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. Center for Devices and Radiological Health; 2009.
7. The International Myotonic Dystrophy Consortium (IDMC). New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). *Neurology*. 2000; 54:1218–1221. [PubMed: 10746587]
8. Griggs RC, Wood DS. Criteria for establishing the validity of genetic recombination in myotonic dystrophy. *Neurology*. 1989; 39:420–421. [PubMed: 2927653]
9. Hilbert JE, Kissel JT, Luebbe EA, Martens WB, McDermott MP, Sanders DB, et al. If you build a rare disease registry, will they enroll and will they use it? Methods and data from the National Registry of Myotonic Dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD). *Contemp Clin Trials*. 2011
10. Muthen, L., Muthen, B. Mplus User's Guide. Muthen & Muthen; Los Angeles, CA: 2006.
11. Cronbach L. Coefficient Alpha and the Internal Structure of Tests. *Psychometrika*. 1951; 16:297–334.
12. McColl, E. Developing Questionnaires. In: Fayers, P., Hays, R., editors. *Assessing Quality of Life in Clinical Trials*. Oxford Press; Oxford: 2005. p. 9–23.
13. Willis, G. Cognitive interviewing and questionnaire design: A training manual. U.S. Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 1994.
14. Harper, P. Myotonic Dystrophy. Saunders Co; Philadelphia, PA: 2001.

15. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures. Statistics and strategies for evaluation. *Control Clin Trials*. 1991; 12:142S–158S. [PubMed: 1663851]
16. Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD. Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value Health*. 2007; 10(Suppl 2):S94–S105. [PubMed: 17995479]
17. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care*. 1989; 27:S217–32. [PubMed: 2646490]
18. Wiklund I, Dimenas E, Wahl M. Factors of importance when evaluating quality of life in clinical trials. *Control Clin Trials*. 1990; 11:169–179. [PubMed: 2163812]
19. Birbeck GL, Kim S, Hays RD, Vickrey BG. Quality of life measures in epilepsy: how well can they detect change over time? *Neurology*. 2000; 54:1822–1827. [PubMed: 10802791]
20. Turner RR, Quittner AL, Parasuraman BM, Kallich JD, Cleeland CS. Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group. Patient-reported outcomes: instrument development and selection issues. *Value Health*. 2007; 10(Suppl 2):S86–93. [PubMed: 17995478]
21. Acquadro C, Berzon R, Dubois D, Leidy NK, Marquis P, Revicki D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. *Value Health*. 2003; 6:522–531. [PubMed: 14627058]
22. Patrick DL, Burke LB, Powers JH, Scott JA, Rock EP, Dawisha S, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. *Value Health*. 2007; 10(Suppl 2):S125–37. [PubMed: 17995471]
23. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013; 309:814–822. [PubMed: 23443445]
24. Mathieu J, Boivin H, Meunier D, Gaudreault M, Begin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. *Neurology*. 2001; 56:336–340. [PubMed: 11171898]
25. Hermans MC, Faber CG, De Baets MH, de Die-Smulders CE, Merkies IS. Rasch-built myotonic dystrophy type 1 activity and participation scale (DM1-Activ). *Neuromuscul Disord*. 2010; 20:310–318. [PubMed: 20363134]
26. Thompson R, Schoser B, Monckton DG, Blonsky K, Lochmuller H. Patient Registries and Trial Readiness in Myotonic Dystrophy--TREAT-NMD/Marigold International Workshop Report. *Neuromuscul Disord*. 2009; 19:860–866. [PubMed: 19846307]
27. Mendell JR, Csimma C, McDonald CM, Escolar DM, Janis S, Porter JD, et al. Challenges in drug development for muscle disease: a stakeholders' meeting. *Muscle Nerve*. 2007; 35:8–16. [PubMed: 17068768]

Figure 1.
Development of the MDHI.

Figure 2.
The test-retest reliability of the MDHI (n=22).

Figure 3.
MDHI Total Score by Known Groups.

Table 1

Demographic and Clinical Characteristics of All Participants

	Group 1	Group 2	Group 3
	Cross-Sectional Study [¶]	Patient Assessment with Qualitative Interviews [‡]	Test-Retest Reliability Study [¥]
Characteristic			
No. of patients studied	278	10	22
Sex, no., (%)			
Male	147 (52.9)	6(60.0)	9(40.9)
Female	128(46.0)	4(40.0)	13(59.1)
Omitted [‡]	3(1.1)	0(0.0)	0(0.0)
Age in years			
Mean, (SD)	47(11.4)	52.2(9.91)	46(13.0)
Range	21–73	34–69	19–69
Genetic test for DM1, no., (%)			
Yes	209(76.0)	4(40.0)	16(72.7)
No	57(20.7)	0(0.0)	6(27.3)
Omitted [‡]	12(4.3)	6(60.0)	0(0)
No. of CTG repeats, mean, (SD)	361(240.9)	305.3(194.7)	371.1(292.3)
No. of CTG repeats, median, (interquartile range)	300(163–530)	271(159–418)	316.5(143–500)
States represented	43 [*]	6	12

^{*} All states represented with the exception of Alaska, Hawaii, Mississippi, Montana, Nevada, North Dakota, and Wyoming.

[‡] Number of times the question was left unanswered by study participants.

[¶] Patient responses used for Question Selection, Factor Analysis, and Question Weighting. One hundred thirty-five participants were assigned approximately 1/2 of the subscales and questions; 143 participants were assigned the remainder of the subscales and questions. Every participant was assigned the original 14 themes questions. All participants were from the PRISM-1 study.

[‡] Each participant reviewed and completed the entire MDHI. Participants recruited through their participation in the Muscular Dystrophy Association Clinic or through prior participation in clinical studies at the University of Rochester.

[¥] Patient responses used to determine the test-retest reliability of the MDHI.

Each participant completed the full MDHI.

All participants were recruited from the NIH-funded DM1 Disease Progression Study (U54NS48843).

Table 2

Final MDHI Subscales and their Internal Consistency and Test-Retest Reliability

MDHI Subscales	Number of Questions in Final Subscale	Internal Consistency (Cronbach's Alpha)	Intraclass Correlation Coefficient (ICC)
a.) Mobility	13	0.98	0.91
b.) Upper Extremity Function	11	0.94	0.92
c.) Ability to do Activities ^a	14	0.95	0.94
d.) Fatigue	4	0.94	0.94
e.) Pain	8	0.93	0.88
f.) Gastrointestinal Issues	6	0.85	0.91
g.) Vision	4	0.82	0.89
h.) Communication	7	0.89	0.87
i.) Sleep ^a	4	0.84	0.76
j.) Emotional Issues	12	0.93	0.91
k.) Cognitive Impairment	9	0.91	0.90
l.) Social Satisfaction ^a	6	0.85	0.97
m.) Social Performance	7	0.90	0.92
n.) Myotonia	4	0.87	0.69
o.) Breathing ^b	1	n/a	0.72
p.) Swallowing ^b	3	0.76	0.81
q.) Hearing ^b	1	n/a	0.97

^aSubscale included questions administered to both halves of Group 1. In each case, all questions but one were answered by the same group. Only questions answered by the same group were used in exploratory factor analyses.

^bExploratory factor analysis (EFA) could not be conducted due to a limited number of items.

Table 3MDHI Total and Subscale Scores by Employment Status and Level of Education ^{a b}

MDHI Subscales	Average Score in DMI (n=278)	Not Employed (n=196)	Employed (n=78)	p-value	College Degree (n=172)	No College Degree (n=101)	p-value
a.) Mobility	46.10	52.58	30.23	<0.01	41.45	55.20	0.02
b.) Upper Extremity Function	41.94	48.18	26.73	<0.01	37.36	51.00	<0.01
c.) Ability to do Activities	43.86	51.11	26.41	<0.01	38.95	53.58	0.01
d.) Fatigue	53.54	58.96	39.92	<0.01	49.42	59.79	0.09
e.) Pain	28.05	31.88	18.62	0.02	23.92	33.16	0.06
f.) Gastrointestinal Issues	25.41	28.58	17.46	0.01	22.91	29.39	0.15
g.) Vision	26.68	31.69	14.18	<0.01	24.71	29.33	0.41
h.) Communication	22.29	25.13	15.34	0.02	18.82	28.92	0.02
i.) Sleep	47.63	51.86	36.43	0.01	46.43	49.76	0.45
j.) Emotional Issues	28.37	33.10	15.95	<0.01	27.19	30.04	0.47
k.) Cognitive Impairment	23.63	26.69	15.69	<0.01	21.65	26.76	0.16
l.) Social Satisfaction	35.84	38.72	28.88	0.09	34.03	39.39	0.24
m.) Social Performance	29.80	34.38	18.76	<0.01	27.59	34.28	0.09
n.) Myotonia	44.87	48.62	35.13	0.03	42.96	47.61	0.34
o.) Breathing	19.46	30.55	8.33	<0.01	16.79	22.77	0.44
p.) Swallowing	27.22	30.35	19.10	0.05	26.58	27.96	0.65
q.) Hearing	12.32	15.75	3.85	<0.01	14.16	10.00	0.29
MDHI Total Score ^c	36.59	41.50	24.98	<0.01	33.8	41.43	<0.01

^aParticipants from the PRISM-1 Study (n=278). Some patients did not report employment status or education and were subsequently not included in the subgroup analysis.^bTo reduce participant burden, all subscales were divided into two surveys. Each participant was randomly assigned to one survey containing all items within a hypothesized subscale.^cCalculated by composite of subscale scores; see text for details.

MDHI Total and Subscale Scores by CTG Repeat Length & Duration of Symptoms ^{a b}**Table 4**

MDHI Subscales	Average Score in DMI (n=278)	CTG 300 (repeat length) (n=60)	CTG <300 (repeat length) (n=55)	p-value	Symptom Duration >20 years (n=106)	Symptom Duration 20 years (n=133)	p-value
a.) Mobility	46.10	43.41	26.87	0.03	58.08	41.16	<0.01
b.) Upper Extremity Function	41.94	44.87	27.52	0.01	48.89	41.20	0.13
c.) Ability to do Activities	43.86	40.47	27.47	0.08	53.1	41.89	0.05
d.) Fatigue	53.54	49.65	44.19	0.63	60.4	48.15	0.04
e.) Pain	28.05	21.88	24.73	0.89	25.46	28.87	0.82
f.) Gastrointestinal Issues	25.41	29.55	19.37	0.08	28.14	24.95	0.29
g.) Vision	26.68	24.37	23.2	0.65	27.52	25.94	0.67
h.) Communication	22.29	22.54	14.81	0.52	26.99	21.59	0.53
i.) Sleep	47.63	48.05	43.57	0.54	52.54	44.12	0.13
j.) Emotional Issues	28.37	28.61	23.44	0.26	28.35	28.59	0.97
k.) Cognitive Impairment	23.63	23.54	21.03	0.70	23.59	23.68	0.95
l.) Social Satisfaction	35.84	33.68	24.84	0.18	41.21	35.66	0.31
m.) Social Performance	29.80	27.49	16.23	0.05	35.06	28.43	0.29
n.) Myotonia	44.87	45.67	37.04	0.34	47.31	42.42	0.38
o.) Breathing	19.46	17.74	14.81	0.91	22.81	16.67	0.12
p.) Swallowing	27.22	26.45	23.79	0.91	29.75	24.66	0.16
q.) Hearing	12.32	16.94	5.77	0.07	14.29	11.59	0.35
MDHI Total Score ^c	36.59	35.56	27.56	<0.01	41.28	34.58	<0.01

^aParticipants from the PRISM-1 Study (n=278).

Some patients did not report CTG repeat length, or duration of symptoms and were subsequently not included in the subgroup analysis.

^bTo reduce participant burden, all subscales were divided into two surveys. Each participant was randomly assigned to one survey.^cCalculated by composite of subscale scores; see text for details.