Myotonic Dystrophy Health Index (MDHI): Measuring Patient-Reported Disease Burden

Myotonic Dystrophy Patient-Centered Therapy Development Workshop
9/17/15

Chad Heatwole, MD, MS-CI

What is the MDHI

- Disease-Specific Patient-Reported Outcome Measure for myotonic dystrophy type-1
- Designed and validated to satisfy all FDA guidelines for drug labeling purposes
- Composed of 17 individual subscales that together measure multifactorial patient-reported burden of disease (*NINDS Common Data Elements*)

What is the MDHI

- Disease-Specific Patient Reported Outcome Measure for myotonic dystrophy type-1
- Designed and validated to satisfy all FDA guidelines for drug labeling purposes
- Composed of 17 individual subscales representing concepts that myotonic dystrophy patients have identified as having the greatest impact on their lives

What does the MDHI Measure? (MDHI Subscales)

- Mobility
- Upper Extremity Function
- Ability to do Activities
- Fatigue
- Pain
- Gastrointestinal Health
- Vision
- Communication
- Hearing
- Sleep
- Emotional Health
- Cognition
- Social Satisfaction
- Social Performance
- Myotonia
- Respiratory Function
- Swallowing
- **Multifactorial Patient-Reported Burden of Disease**

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 (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

Table 2. Measurement Properties Considered in the Review of PRO Instruments Used in Clinical Trials

Measurement Property	Type	What Is Assessed?	FDA Review Considerations
Reliability	Test-retest or intra-interviewer reliability (for interviewer-administered PROs only)	Stability of scores over time when no change is expected in the concept of interest	• Intraclass correlation coefficient • Time period of assessment
	Internal consistency	• Extent to which items comprising a scale measure the same concept • Intercorrelation of items that contribute to a score • Internal consistency	• Cronbach's alpha for summary scores • Item-total correlations
	Inter-interviewer reliability (for interviewer-administered PROs only)	Agreement among responses when the PRO is administered by two or more different interviewers	• Interclass correlation coefficient
Validity	Content validity	Evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity.	• Derivation of all items • Qualitative interview schedule • Interview or focus group transcripts • Items derived from the transcripts • Composition of patients used to develop content • Cognitive interview transcripts to evaluate patient understanding
	Construct validity	Evidence that relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient groups	• Strength of correlation testing *a priori* hypotheses (discriminant and convergent validity) • Degree to which the PRO instrument can distinguish among groups hypothesized *a priori* to be different (known groups validity)
Ability to detect change		Evidence that a PRO instrument can identify differences in scores over time in individuals or groups (similar to those in the clinical trials) who have changed with respect to the measurement concept	• Within person change over time • Effect size statistic

Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1)

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ABSTRACT

Objective: To determine the most critical symptoms in a national myotonic dystrophy type 1 (DM1) population and to identify the modifying factors that have the greatest effect on the severity of these symptoms.

Methods: We performed a cross-sectional study of 278 adult patients with DM1 from the national registry of patients with DM1 between April and August 2010. We assessed the prevalence and relative significance of 221 critical DM1 symptoms and 14 disease themes. These symptoms and themes were chosen for evaluation based on prior interviews with patients with DM1. Responses were categorized by age, CTG repeat length, gender, and duration of symptoms.

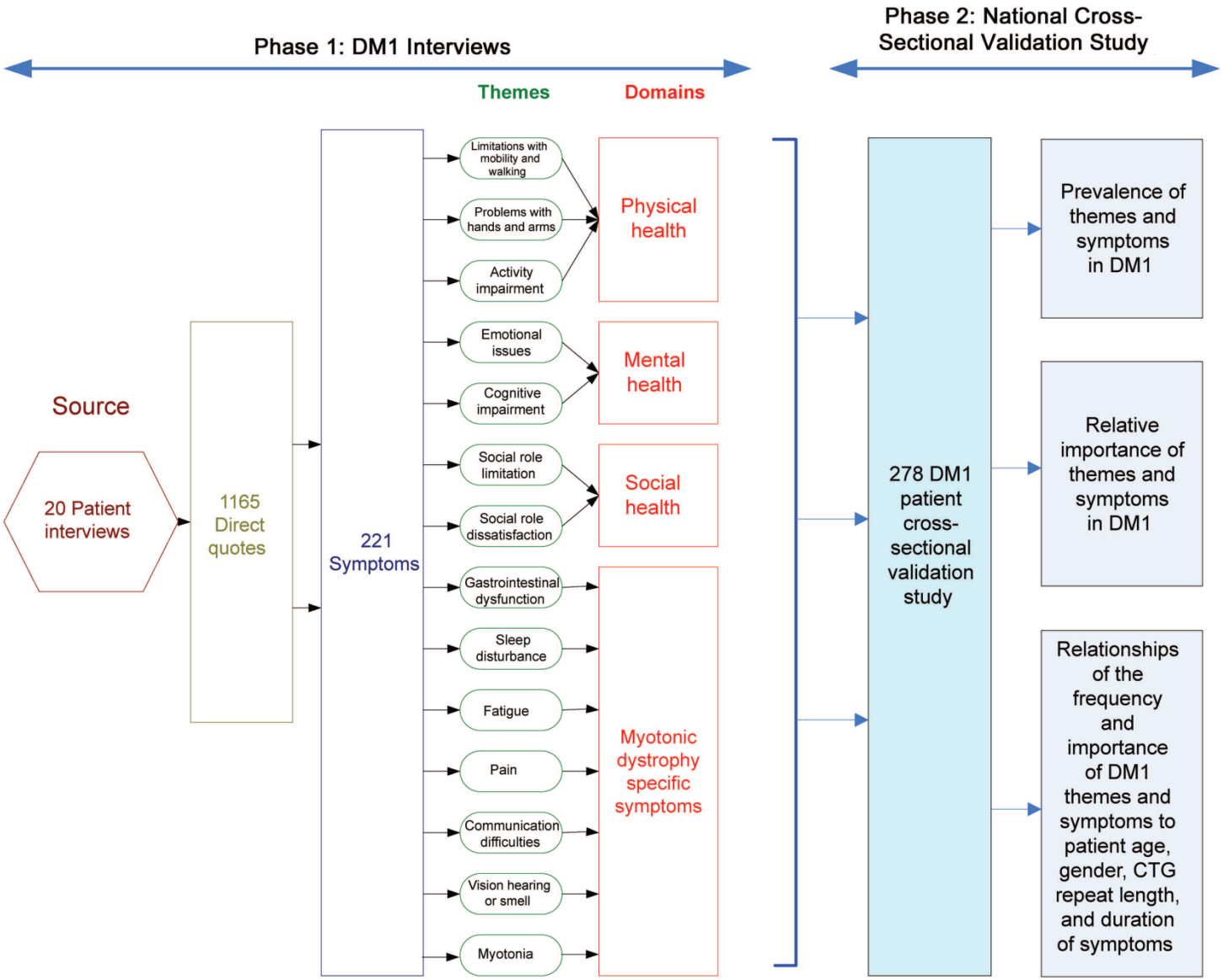
Results: Participants with DM1 provided symptom rating survey responses to address the relative frequency and importance of each DM1 symptom. The symptomatic themes with the highest prevalence in DM1 were problems with hands or arms (93.5%), fatigue (90.8%), myotonia (90.3%), and impaired sleep or daytime sleepiness (87.9%). Participants identified fatigue and limitations in mobility as the symptomatic themes that have the greatest effect on their lives. We found an association between age and the average prevalence of all themes ($p < 0.01$) and between CTG repeat length and the average effect of all symptomatic themes on participant lives ($p < 0.01$).

Conclusions: There are a wide range of symptoms that significantly affect the lives of patients with DM1. These symptoms, some previously underrecognized, have varying levels of importance in the DM1 population and are nonlinearly dependent on patient age and CTG repeat length. *Neurology*® 2012;79:1–1

GLOSSARY

DM1 = myotonic dystrophy type 1; **FDA** = Food and Drug Administration; **FSHD** = facioscapulohumeral muscular dystrophy; **PRISM-1** = Patient Reported Impact of Symptoms in Myotonic Dystrophy Type 1.

AQ: 1


Phase 1: DM1 Interviews
Phase 2: National Cross-Sectional Validation Study
Themes
Domains
Source
20 Patient interviews
1165 Direct quotes
221 Symptoms
Limitations with mobility and walking
Problems with hands and arms
Activity impairment
Emotional issues
Cognitive impairment
Social role limitation
Social role dissatisfaction
Gastrointestinal dysfunction
Sleep disturbance
Fatigue
Pain
Communication difficulties
Vision hearing or smell
Myotonia
Physical health
Mental health
Social health
Myotonic dystrophy specific symptoms
278 DM1 patient cross-sectional validation study
Prevalence of themes and symptoms in DM1
Relative importance of themes and symptoms in DM1
Relationships of the frequency and importance of DM1 themes and symptoms to patient age, gender, CTG repeat length, and duration of symptoms

MUSCLE & NERVE

Muscle Nerve. 2013 Oct 19. doi: 10.1002/mus.24097. [Epub ahead of print]

The myotonic dystrophy health index: Initial evaluation of a new outcome measure.

Heatwole C, Bode R, Johnson N, Dekdebrun J, Dilek N, Heatwole M, Hilbert JE, Luebbe E, Martens W, McDermott MP, Rothrock N, Thornton C, Vickrey BG, Victorson D, Moxley R 3rd.

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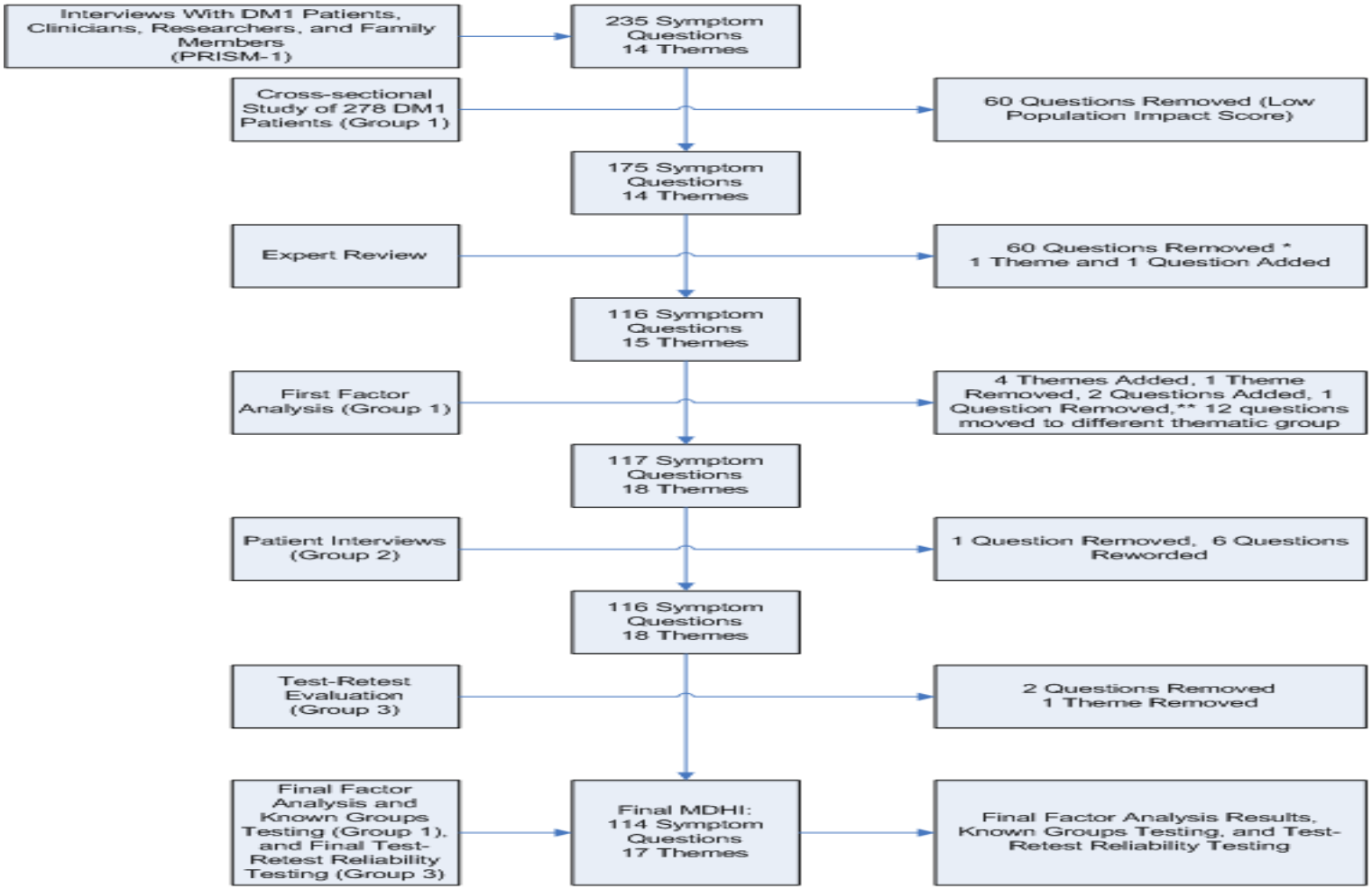
Abstract

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. © 2013 Wiley Periodicals, Inc.

Figure e-1: Development of the MDHI



* 31 questions excluded due to low responsiveness
15 questions excluded due to vague wording
6 questions excluded due to redundancy
5 questions excluded due to being potentially offensive
2 questions excluded due to being tied to affluence
1 question excluded due to wording requiring a high vocabulary

**New Themes: 1) Breathing Difficulties; 2) Choking or Swallowing Issues; 3) Problems with Vision; 4) Hearing Difficulties
Removed theme/question: Problems with Vision, Hearing, or Smell
New Questions: 1) Problems with Vision; 2) Choking and Swallowing Issues

Figure 1: The Test-Retest Reliability of the MDHI

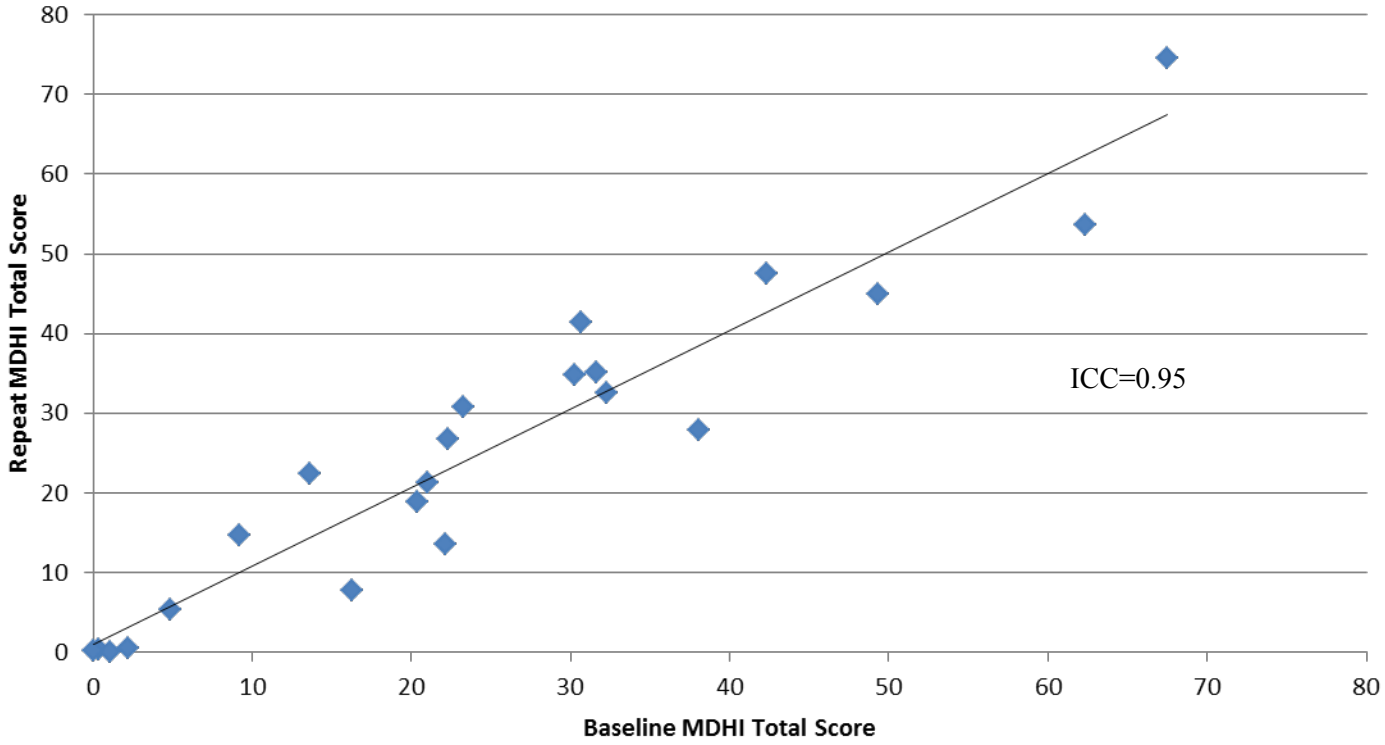
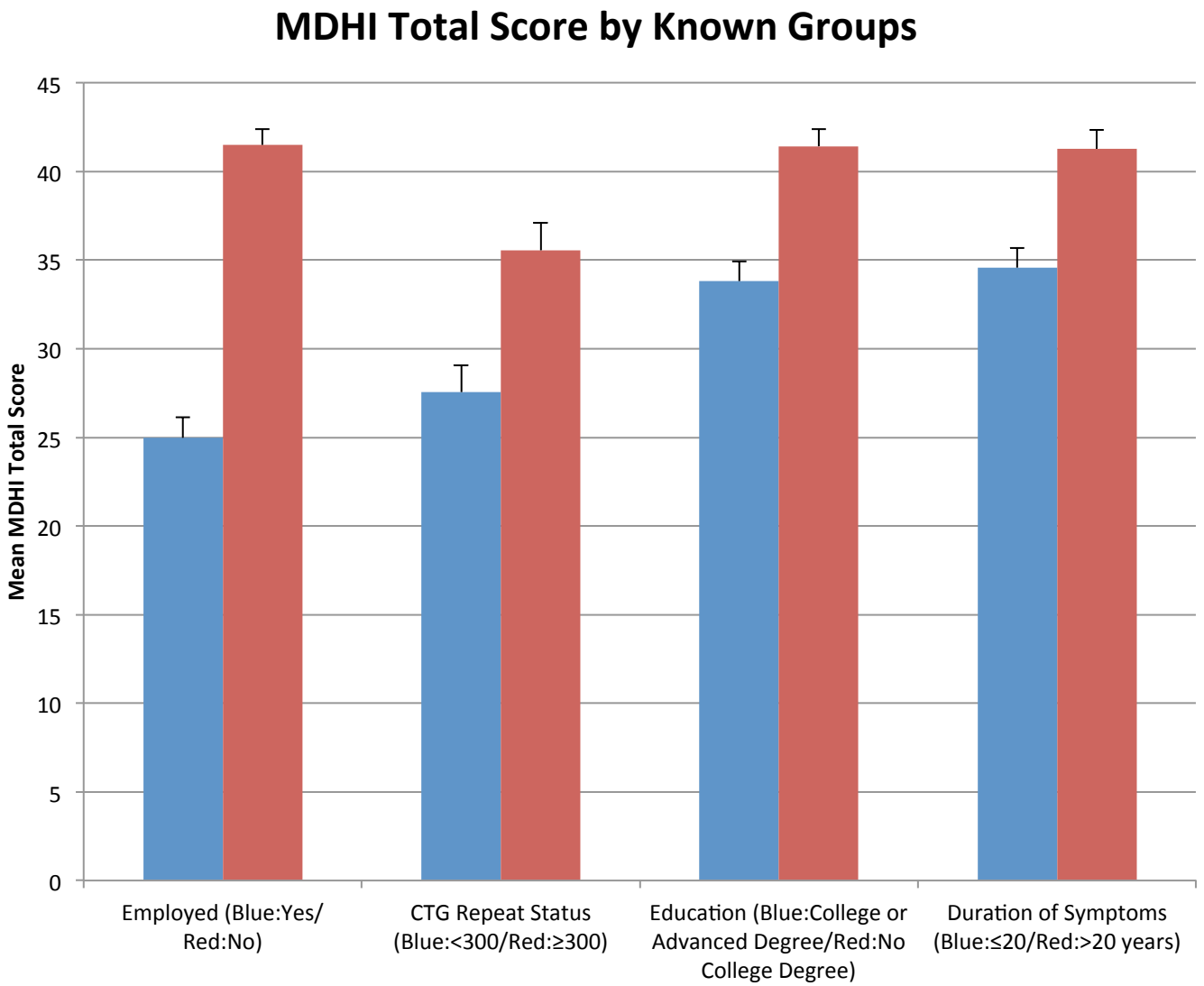


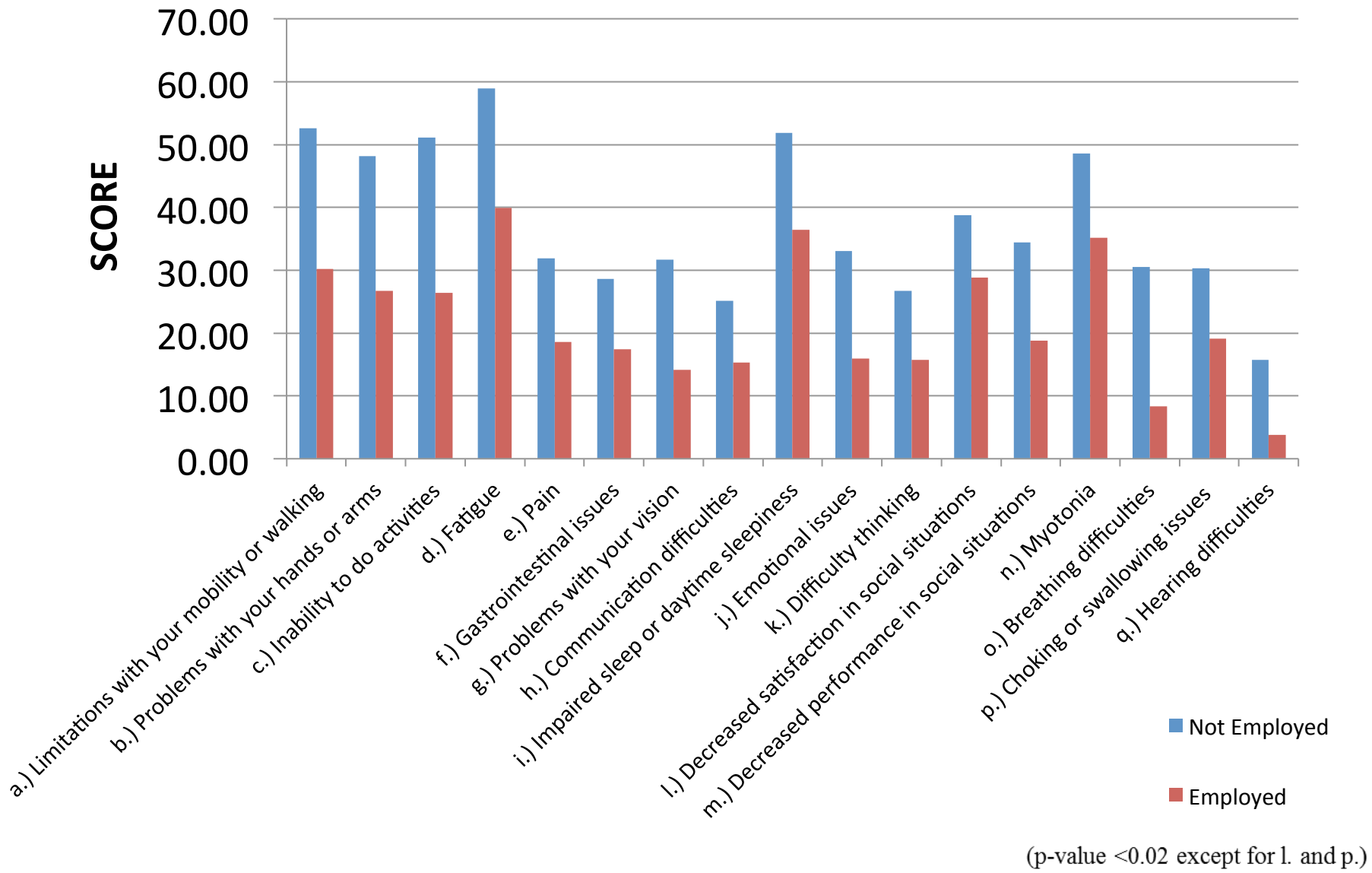
Table 2: Final MDHI Subscales and their Internal Consistency and Test-Retest Reliability		
MDHI Subscales	**Number of Questions in Final Subscale**	**Intraclass Correlation Coefficient (ICC)**
a.) Mobility	13	0.91
b.) Upper Extremity Function	11	0.92
c.) Ability to do Activities [a]	14	0.94
d.) Fatigue	4	0.94
e.) Pain	8	0.88
f.) Gastrointestinal Issues	6	0.91
g.) Vision	4	0.89
h.) Communication	7	0.87
i.) Sleep [a]	4	0.76
j.) Emotional Issues	12	0.91
k.) Cognitive Impairment	9	0.90
l.) Social Satisfaction [a]	6	0.97
m.) Social Performance	7	0.92
n.) Myotonia	4	0.69
o.) Breathing [b]	1	0.72
p.) Swallowing [b]	3	0.81
q.) Hearing [b]	1	0.97

MDHI Question Distribution: Internal Consistency (17 Subscales)

DM1 Specific Subscales	Number of Questions in Subscale (total= 114)	Internal consistency (Cronbach's alpha)
a.) Limitations with your mobility or walking	13	0.977
b.) Problems with your hands or arms	11	0.941
c.) Inability to do activities	14	0.949
d.) Fatigue	4	0.940
e.) Pain	8	0.933
f.) Gastrointestinal issues	6	0.849
g.) Problems with your vision	4	0.816
h.) Communication difficulties	7	0.889
i.) Impaired sleep or daytime sleepiness	4	0.837
j.) Emotional issues	12	0.933
k.) Difficulty thinking	9	0.910
l.) Decreased satisfaction in social situations	6	0.854
m.) Decreased performance in social situations	7	0.903
n.) Myotonia	4	0.874
o.) Breathing difficulties	1	n/a
p.) Choking or swallowing issues	3	0.758
q.) Hearing difficulties	1	n/a


MDHI Total Score by Known Groups
Mean MDHI Total Score
45
40
35
30
25
20
15
10
5
0
Employed (Blue:Yes/ Red:No)
CTG Repeat Status (Blue:<300/Red:≥300)
Education (Blue:College or Advanced Degree/Red:No College Degree)
Duration of Symptoms (Blue:≤20/Red:>20 years)

MDHI Subscale Scores by Employment Status



(p-value <0.02 except for l. and p.)

COMFORT Study (Construct and Convergent Validity)

- Comparison of MDHI with Functional and Other Research Testing (COMFORT)
- A cross-sectional study of DM1 patients comparing MDHI scores to 25 functional tests, six laboratory tests, 18 generic patient reported outcome assessments, and seven physician assessments
- Completed as part of our: Study of Pathogenesis and Progression in Dystrophia Myotonica (STOPP DM) Wellstone study

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Conclusion

- The MDHI is a disease-specific, valid, responsive, and reliable instrument designed to optimally measure patient-reported disease-burden during clinical trials.

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MYOTONIC DYSTROPHY FOUNDATION

Connecting people with researchers

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MDA Muscular Dystrophy Association

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health

FIELDS FSHD & Neuromuscular Research CENTER

University of Rochester Medical Center

LUMC Leiden University Medical Center

NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institutes of Health, Department of Health and Human Services

THE GREAT SEAL OF THE STATE OF NEW YORK EXCELSIOR

The Neuromuscular Institute of Quality-of-Life Studies and Outcome Measure Development