A Novel Measure to Assess Self-Reported Physical Functioning in Patients With Sporadic Inclusion Body Myositis

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BACKGROUND

Patient-Reported Outcomes (PROs)

- PROs describe the impact of health conditions and treatments on patient lives from the perspective of patients directly, without interpretation from health care professionals or other sources.[1]
- As such, PROs provide important insight into the patient experience of a disease or therapy that otherwise may not be obtained by clinical measures alone.
- PRO data are collected via standardized questionnaires designed to measure an explicit concept or construct such as symptoms, activity limitations, and health status/health-related quality of life.
- The instruments used to capture PROs are collectively referred to as PRO measures.

Sporadic Inclusion Body Myositis (sIBM)

- sIBM is a progressive, idiopathic inflammatory myopathy characterized by atrophy and weakness of proximal and distal muscle groups.
  - Atrophy of the quadriceps, wrist, and finger flexor muscles, as well as dysphagia are clinical hallmarks of the disease and result in significant functional disabilities with progression.
  - sIBM primarily affects individuals aged older than 50 years and is more common in men than in women.
  - Symptoms worsen over time, causing most patients to eventually lose ambulatory status and the ability to perform many routine activities of daily living.
- Currently, there are no marketed therapies for the treatment of sIBM.
- Promising clinical trials are underway, and well-defined and reliable outcome assessments for physical functioning specific to sIBM are needed to demonstrate meaningful treatment benefit of new therapies.

Measures of Functional Impairment and Disability

- Measures of functional impairment and disability can be either performance based or self-reported.
  - While both methods offer important insights, self-report allows patients to consider their real-world experiences integrated over time, which provides greater insight into the patient's functioning and is not limited to a single-objective measure,[2] as well as to express important elements of functional impairment.
  - There is a need for well-developed and valid PRO measures of physical functioning in order to best demonstrate treatment benefit from the patient perspective.

OBJECTIVE

- To develop a well-defined and reliable patient-reported measure of physical functioning in accordance with the FDA PRO guidance for use in patients with sIBM, the sIBM Sporadic Inclusion Body Myositis Physical Functioning Assessment (sIFA).

METHODS

Literature Review

- A search of published literature indexed on PubMed was conducted to identify existing measures and concepts relevant for measurement in sIBM studies.
  - Articles published from January 2002 to March 2012 were identified for potential inclusion based on a predefined set of search criteria.
    - Studies that were conducted with adults in clinical trials, observational studies, longitudinal studies, naturalistic studies, cross-sectional studies, retrospective or prospective cohort analyses, systematic literature reviews, surveys, or instrument validation studies
    - Studies published in English
    - Studies published since 2002
    - Other papers identified as seminal by the authors
  - PRO measures identified in this initial search were evaluated for inclusion in the review based on their relevance.
    - Measures were reviewed if they were developed for patients with a diagnosis of sIBM and/or if they assessed constructs related to the assessment of symptoms and the impact of sIBM on patient physical functioning.

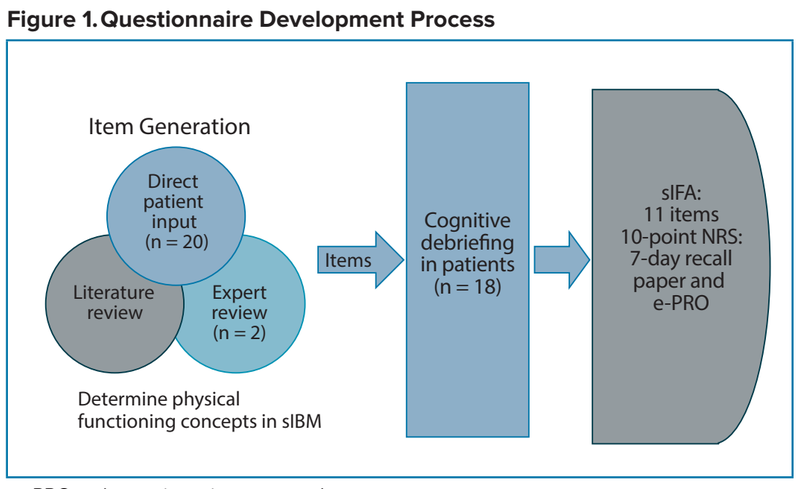
Expert Input

- Expert input was obtained from two clinician experts on the following.
  - Experts were interviewed via teleconference to further inform concept identification.
  - Experts were asked to provide insight and clinical input:
    - Impact of sIBM on patients
    - Approaches to the measurement of sIBM treatment benefit relative to physical functioning

Patient Input

- A single-visit, observational study involving in-depth concept elicitation interviews was conducted in Philadelphia, PA, and Columbus, OH.
  - Twenty patients across a range of functional limitation were included.
  - Participants met the following criteria:
    - Confirmed clinical diagnosis of sIBM (per Hilton-Jones or European Neuromuscular Centre criteria)
    - Aged 35-80 years
    - Able to read and understand English
    - Willing to participate in a 1-hour interview to discuss experiences related to sIBM
- Interviewers followed a semistructured discussion guide, and the same two experienced interviewers conducted all participant interviews.
- A draft item pool was constructed including multiple items representing each concept:
  - Developed with several differing response scales:
    - Numerical rating scale (NRS)
    - Verbal rating scale
- To test and further refine the long-list questionnaire, a total of 18 individual cognitive debriefing interviews were conducted in a new sample of patients with sIBM.
  - Participant feedback was used to modify and refine question wording to improve the comprehensibility of each item.
  - Edits were made to both the instructions and the individual items to improve consistency in respondent interpretation.
  - Best candidate items and scales were selected for inclusion in the draft measure.
  - Following cognitive debriefing, a final round of expert physician review was sought.
- An electronic (tablet) version of the sIFA was designed and successfully tested with patients.
- Figure 1 depicts this process.

Figure 1. Questionnaire Development Process



e-PRO = electronic patient-reported outcome measure.

RESULTS

Literature Review

- A summary of symptoms, impacts related to physical functioning, and psychosocial impacts were identified.
- Symptoms relating to progressive weakness and atrophy of the quadriceps, wrist, and finger flexor muscles were identified as the clinical hallmarks of sIBM[3-6]:
  - Grip strength and fine motor skills
  - Frequent falls
  - Progressive weakness
  - Generalized sensory peripheral neuropathy in some patients
  - Foot drop
  - Difficulty standing from a sitting position
  - Dysphagia: swallowing difficulties, choking, interference with nutritional intake
- Review of the literature identified only one patient-reported measure developed and validated specifically to assess functioning and impact of sIBM, the Inclusion Body Myositis-Functional Rating Scale (IBM-FRS).
  - The IBM-FRS is a 10-item sIBM-specific functional rating scale that was derived as a modification of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS).
  - ALS-FRS items that were not applicable to sIBM were substituted or modified with new questions developed by the authors.
  - The measure was developed prior to the release of the FDA PRO guidance and was not specific for use in sIBM clinical trials.

Expert Input

- Expert input supported the findings from the literature review.
- Experts noted that patients often initially present with leg weakness and describe instances of their knees "buckling" or collapsing without warning.
  - Complaints of falls are often one of the earliest signs of the disease.
  - Concerns with finger dexterity are reported.
  - Atrophy of the quadriceps and forearm muscles, often asymmetrical, is typical.
    - Appearance of foot drop is typical.
    - Upper and lower extremity weakness can present separately or simultaneously.
  - Functional impacts are a clear testament to the clinical presentation of sIBM.
    - Earliest impacts reported to physicians include impaired ambulation (including fatigue when walking), weakness getting up from a chair, and foot drop.
    - Reported impacts related to activities of daily living included shopping and using the toilet.
    - As the disease progresses, patients require use of a walker and then a wheelchair.

Patient Input

- Twenty individual concept elicitation interviews (Tables 1 and 2) were conducted with patients with sIBM from June through September 2012.
- Five high-level concepts were explored:
  - Symptoms
  - Physical functioning
  - Psychosocial impact
  - Objective measures
  - Treatment expectations
- A long-list of questionnaire items was generated directly from the concepts captured during the patient interview process.
- Figure 2 depicts a conceptual framework for the sIFA developed in part through analysis of dominant themes discovered in the literature and through consultation with clinicians but based mainly on the input of patients with sIBM.
  - The conceptual framework describes the expected relationships of items within a domain and expected relationships among domains within a PRO concept.[7]
- Table 3 provides the demographics for this sample (n = 18).
  - Participants readily endorsed all concepts as very relevant and important to the assessment of physical functioning.
  - Participants did not identify any physical functioning items as missing.
- The resultant PRO measure consists of 11 items scored on a 0 (no difficulty) to 10 (unable to do) NRS. sIFA items are aligned with the functional impact of sIBM as described in the literature and expert review, as well as identified as relevant and important to sIBM patients.

Table 1. Characteristics of Concept Elicitation Interview Participants

Characteristic	N = 20
Age at diagnosis, mean (range)	58.5 years (41-79 years)
Age at interview, mean (range)	66.9 years (46-81 years)
Sex, n (%)	
Male	18 (90.0%)
Female	2 (10.0%)
Education, n (%)[a]	
High school or equivalent (e.g., GED)	4 (21.1%)
Some college	4 (21.1%)
College degree	4 (21.1%)
Professional or advanced degree	7 (36.8%)
Race/ethnicity, n (%)	
White	18 (90.0%)
Asian	1 (5.0%)
Black	1 (5.0%)

GED = general education diploma.

[a] Education not available for 1 participant.

Table 2. Category Best Describing Current Level of Limitation

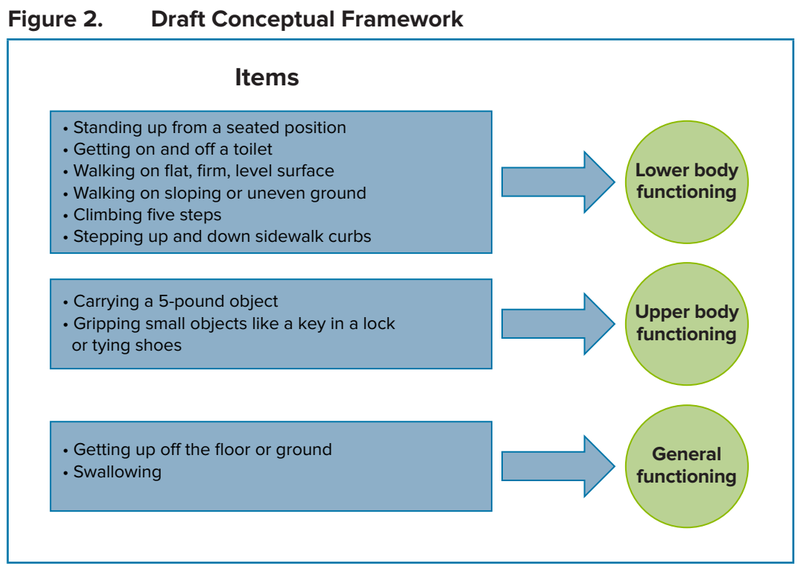
Current Level of Limitation[a]	n (%)
Increased muscular weakness, particularly of the thigh muscles and forearms	3 (15.8%)
Decreased ability to perform certain activities, including writing, opening jars, standing from a seated position	2 (10.5%)
Impaired walking (tripping or falling)	2 (10.5%)
Use of cane when walking	3 (15.8%)
Use of a walker	3 (15.8%)
Use of a wheelchair	6 (31.6%)

[a] Current level of limitation not available for 1 participant.

Table 3. Characteristics of Cognitive Debriefing Interview Participants

Characteristic	N = 18
Age at interview, mean (range)	69.4 years (52-90)
Sex, n (%)	
Male	10 (55.0%)
Female	8 (45.0%)
Education, n (%)	
High school or equivalent (e.g., GED)	2 (11.1%)
Some college	3 (16.6%)
College degree	8 (44.4%)
Professional or advanced degree	5 (27.8%)
Race/ethnicity, n (%)	
White	18 (100.0%)
Category best describing current level of limitation, n (%)	
Increased muscular weakness, particularly of the thigh muscles and forearms	0 (0%)
Decreased ability to perform certain activities including writing, opening jars, standing from a seated position	3 (16.6%)
Impaired walking (tripping or falling)	4 (22.2%)
Use of cane when walking	1 (5.0%)
Use of a walker	7 (38.8%)
Use of a wheelchair	2 (11.1%)

Figure 2. Draft Conceptual Framework



CONCLUSIONS

- Extensive research aligned with the FDA PRO guidance resulted in the development of the sIFA.
- The sIFA is designed to be self-administered, gathering direct patient input without the influence of others, and is intended to assess change after treatment in a standardized manner.
  - Items are scored on an 11-point NRS.
  - Recall period is the "last 7 days" to allow for accurate patient feedback.
- Two modes of administration are available: pen and paper and e-PRO tablet.
- Importantly, to our knowledge, this is the only such tool to be developed in accordance with the FDA PRO guidance recommendations for use in clinical trials.
- A rigorous psychometric evaluation of the sIFA is underway to supplement the content validity of the new tool and to demonstrate key measurement properties.

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