Development and Validation of the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS™)

PRM84

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INTRODUCTION

Background

- Multiple sclerosis (MS), an inflammatory autoimmune disorder of the central nervous system (CNS), is the most common cause of progressive neurological disability in young adults.[1, 2]
- Variable patterns of disease activity are observed in MS, including 3 different disease courses in relapsing MS (RMS):[2]
  - Relapsing-remitting MS (RRMS): acute exacerbations with full or partial recovery, stable between exacerbations (~80%–85% of MS patients)
  - Progressive-relapsing MS (PRMS): progression starting at disease onset, with occasional relapses (~5% of MS patients)
  - Relapsing secondary-progressive MS (RSPMS): gradual progression of disability later in the disease course of RRMS patients (~65%–70% of RRMS patients)
- Common symptoms of MS that affect patient quality of life are fatigue, visual impairment, difficulties with arm coordination, bowel and bladder dysfunction, speech problems, difficulty swallowing, pain, and symptoms of depression.[3] Fatigue is the most common symptom of MS impacting patients' mental and physical health.[4, 5]
- Given the subjective nature of fatigue, the effect of treatment on fatigue in MS is best assessed via a patient-reported outcome (PRO) instrument.[6]
- The US Food and Drug Administration's (FDA) PRO Guidance for Industry (2009)[7] emphasizes the importance of documenting content validity of PROs, including evidence that an instrument is conceptually comprehensive, relevant, and understandable to patients.
- PRO instruments commonly used to measure fatigue in MS were developed prior to publication of the FDA PRO guidance in 2009, and do not satisfy modern standards of outcome measurement.[8]

Objectives

- To develop a new PRO instrument to assess fatigue symptoms relevant to patients with RRMS and the impacts of these symptoms on patients' lives, in accordance with the FDA PRO guidance.
- To assess whether the PRO instrument was adequate to measure fatigue-related symptoms and their impacts in patients with PRMS and RSPMS.

METHODS

- A cross-sectional, qualitative research study was undertaken consisting of distinct study phases (Figure 1):
  - Concept elicitation interviews of RRMS patients were conducted to better understand the patients' experience of their disease, and inform the development of a new PRO instrument
  - Cognitive interviews were conducted with RRMS patients to test the face and content validity of the newly developed PRO instrument and revise it if required
  - Content confirmation interviews were conducted with PRMS and RSPMS patients to evaluate the content validity of the PRO instrument in these patient populations

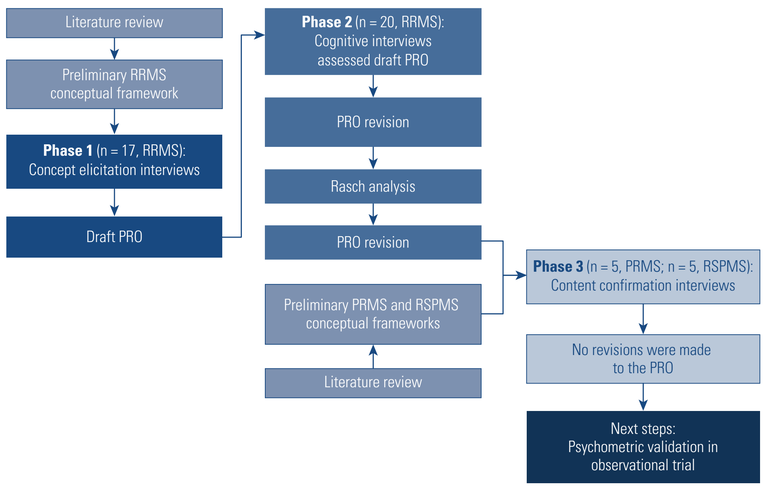

Figure 1. Study flow *PRO: patient-reported outcomes; PRMS: progressive-relapsing MS; RRMS: relapsing-remitting MS; RSPMS: relapsing secondary-progressive MS.*

- Prior to initiating the qualitative research, a literature review was conducted to inform development of a preliminary conceptual framework to document the fatigue-related symptoms of RRMS and their impacts.
- Following the development of a study protocol and a semi-structured interview guide, study documents were submitted to a centralized Institutional Review Board for ethical approval.
- Patients meeting study eligibility criteria (Table 1) were recruited by two commercial recruitment agencies from 7 clinical sites across the US.

Table 1. *Study eligibility criteria*

Study phase	Inclusion criteria	Exclusion criteria
All	■ Age ≥18 years ■ Completed written ICF ■ Ambulatory ■ Fluent in US English ■ Capable of participating in a 90-minute face-to-face interview	■ Any condition that may result in energy- or fatigue-related symptoms (other than RMS), including but not limited to congenital or acquired immunodeficiency or known HIV infection, malignancy, and poorly controlled diabetes ■ Current treatment for an autoimmune disorder other than MS ■ Any condition or situation that may interfere significantly with study participation
Phase 1: Concept elicitation interviews	■ RRMS diagnosis as defined by the revised McDonald Diagnostic Criteria for MS[9]	
Phase 2: Cognitive interviews	■ At least one of the following: – ≥1 documented relapse in the last 12 months – ≥2 documented relapses in the last 24 months ■ EDSS score[10, 11] of 0–5.5 in the past 6 months ■ Stable course since EDSS assessment	
Phase 3: Content confirmation interviews	■ Age ≤65 years ■ RMS diagnosis as defined by the revised McDonald Diagnostic Criteria for MS[9] ■ PRMS or RSPMS diagnosis ■ EDSS[10, 11] score of 3–5.5 in the past 6 months ■ Documented relapse during prior 12 months	■ RRMS diagnosis

COPD: chronic obstructive pulmonary disease; EDSS: Expanded Disability Status Scale; ICF: subject information and consent form including authorization to use and disclose personal health information for research; HIV: human immunodeficiency virus; MS: multiple sclerosis; PRMS: progressive-relapsing MS; RMS: relapsing MS; RRMS: relapsing-remitting MS; RSPMS: relapsing secondary-progressive MS.

- Recruitment aimed to enroll a sample generally representative of the epidemiology of the RMS population likely to be enrolled in future clinical trials.
- Each face-to-face interview was audio-recorded, transcribed by a third-party transcription agency, and anonymized prior to analysis.
- Qualitative analysis was conducted using ATLAS.ti qualitative data analysis software (ATLAS.ti Scientific Software Development GmbH, Berlin). Each interview transcript served as 1 unit of analysis, and transcripts were coded in ATLAS.ti to "tag" patient quotes relevant to the research question.
- Coded transcripts were used to generate comprehensive findings tables of all relevant patient quotes elicited during each study phase.

Phase 1: RRMS concept elicitation interviews (n = 17) and item generation

- Face-to-face interviews were conducted with RRMS patients using a semi-structured interview guide. Patients were asked open-ended questions to spontaneously elicit fatigue-related symptoms of RRMS and their impacts as experienced by the patient; additional, probing questions were posed if the initial open-ended queries did not elicit a meaningful response from patients (i.e., an explicit description of a fatigue-related symptom or impact).
- Following qualitative analysis of the interview transcripts, concept saturation was assessed. Saturation was considered to be achieved at the point at which no new, relevant concepts (for both fatigue and its impacts) emerged from interviews.
- A sample size of 15 patients was anticipated to be sufficient to achieve saturation. An additional two patients were recruited to account for no-shows and/or cancellations.
- Based on the spontaneously elicited concepts in the interviews, items for the new PRO instrument were generated by the investigators. In particular, special attention was given to the frequency with which a concept was spontaneously reported (i.e., concepts spontaneously reported by >5 [29.4%] patients).
- The items comprising the initial draft were developed according to the requirements of the FDA PRO Guidance; as such, items were designed to:
  - Represent a single, unique concept
  - Be relevant to patients with RRMS
  - Eschew medical terms and value-laden words
  - Avoid double-enquiry
  - Be worded consistently with the instrument's response options
  - Measure a concept likely to change with successful treatment
  - Be unlikely to be vulnerable to ceiling or floor effects within the target population.

Phase 2: Cognitive debriefing interviews with RRMS patients (n = 20)

- Following development of the draft PRO instrument, an additional sample of 20 RRMS patients participated in face-to-face cognitive interviews designed to better understand how patients interpret and use the instrument to select responses.
- During these interviews, interviewers asked patients to complete the instrument and subsequently used a semi-structured interview guide to obtain feedback on the instrument. Specifically, patients were asked questions regarding the:
  - Relevance, comprehensibility, acceptability, and comprehensiveness of the instrument items
  - Interpretability and appropriateness of the instructions, response options, and recall period.
- Patient responses were tabulated for each item in the draft PRO. Revisions were deemed necessary if ≥5 (or at least 25.0%) of patients reported consistent recommendations for revisions (e.g., rewording, deletion, or addition of items) or demonstrated difficulty with interpretation or did not interpret items as intended.

Phase 3: Content confirmation interviews (n = 5 PRMS interviews, n = 5 RSPMS interviews)

- Following completion of the cognitive interviews in RRMS patients, additional interviews were conducted with patients with RSPMS and PRMS to test the relevance of the instrument in these populations.
- Initially, conceptual frameworks were developed, based on a literature review, to document the fatigue-related symptoms of RSPMS and PRMS and their impacts.
- One-on-one interviews were conducted with RSPMS and PRMS patients and consisted of both a concept elicitation and cognitive interviewing sections. Both sections of these interviews were conducted using the same methodology as the interviews conducted during Phases 1 and 2.
- Data were analyzed in the same manner as the respective concept elicitation and cognitive interviewing data collected during Phases 1 and 2.
- Transcribed interview data were used to confirm the concepts included in the draft PRO instrument, and to assess whether any revisions, deletions, or additions were required. In addition, the ability of patients to understand and use the instrument was determined.

RESULTS

Patient sample

- A total of 47 patients were recruited from 7 clinical sites across study phases. (Table 2)
- Patients were predominantly female across study phases, and were of diverse age, race/ethnicity, work status, educational level, and MS disease severity (Table 3).

Table 2. *Study sites*

Phase	City	Number of patients
Phase 1: Concept elicitation in RRMS patients	Des Plaines, IL	5
	Encino, CA	6
	Metairie, LA	6
Phase 2: Cognitive interviews in RRMS patients	Encino, CA	8
	St. Paul, MN	5
	Earth City, MO	7
Phase 3: Content confirmation in PRMS and RSPMS patients	Baltimore, MD	6
	Oak Lawn, IL	4

PRMS: progressive-relapsing MS; RMS: relapsing MS; RRMS: relapsing-remitting MS; RSPMS: relapsing secondary-progressive MS.

Table 3. *Characteristics of study patients*

Characteristic	Phase 1 RRMS (n = 17)	Phase 2 RRMS (n = 20)	Phase 3 PRMS (n = 5)	Phase 3 RSPMS (n = 5)	Total (N = 47)
Age, years, mean ± SD (range)	43.9±13.34 (27–75)	47.0±12.0 (25–69)	52.6±12.5 (34–67)	52.4±10.8 (38–63)	47.0±12.4 (25–75)
Female:male, n (%)	13:4 (76.5:23.5)	16:4 (80:20)	4:1 (80:20)	3:2 (60:40)	36:11 (76.6:23.4)
Race/ethnicity, n (%)					
Caucasian	13 (76.5)	17 (85)	2 (40)	4 (80)	36 (76.6)
African American	2 (11.8)	3 (15)	3 (60)	1 (20)	9 (19.1)
Asian	1 (5.9)	0	0	0	1 (2.1)
American Indian or Alaskan Native	1 (5.9)	0	0	0	1 (2.1)
Work status, n (%)*					
Working full-time	6 (35.3)	8 (40)	1 (20)	0	15 (31.9)
Working part-time	1 (5.9)	0	1 (20)	0	2 (4.3)
Homemaker	1 (5.9)	3 (15)	0	0	4 (8.5)
Student	3 (17.6)	0	0	0	3 (6.4)
Retired	3 (17.6)	5 (25)	1 (20)	1 (20)	10 (21.3)
Unemployed	6 (35.3)	3 (15)	0	0	9 (19.1)
Other – Disability	4 (23.5)	3 (15)	2 (40)	4 (80)	13 (27.7)
Highest level of education, n (%)					
High school diploma or GED	1 (5.9)	2 (10)	0	1 (20)	4 (8.5)
Some college or certificate program	4 (23.5)	8 (40)	2 (40)	2 (40)	16 (34.0)
College or university degree	8 (47.1)	9 (45)	1 (20)	2 (40)	20 (42.6)
Graduate degree	4 (23.5)	1 (5)	2 (40)	0	7 (14.9)
MS severity					
Very mild	1 (5.9)	4 (20)	0	0	5 (10.6)
Mild	7 (41.2)	7 (35)	1 (20)	2 (40)	17 (36.2)
Moderate	9 (52.9)	9 (45)	4 (80)	2 (40)	24 (51.1)
Severe	0	0	0	1 (20)	1 (2.1)
EDSS score, n (%)†					
0.0–1.0	4 (23.5)	4 (20)	–	–	8 (17.0)
1.5–2.0	2 (11.7)	4 (20)	–	–	6 (12.8)
2.5–3.0	4 (23.5)	4 (20)	0	0	8 (17.0)
3.5–4.0	5 (29.4)	6 (30)	3 (60)	1 (20)	15 (31.9)
4.5–5.0	1 (5.8)	0	2 (40)	0	3 (6.4)
5.5–6.0	1 (5.8)	2 (10)	0	4 (80)	7 (14.9)

*EDSS: Expanded Disability Status Scale; PRMS: progressive-relapsing MS; RRMS: relapsing-remitting MS; RSPMS: relapsing secondary-progressive MS. *Counts are not mutually exclusive. †Inclusion criteria for Phase 3 interviews indicates that patients must have had an EDSS score of 3.0 to 5.5 for participation.*

Phase 1: Concept elicitation interviews (n = 17) and item generation

- Analysis revealed that the number of interviews conducted was sufficient to reach saturation, with no new concepts spontaneously elicited in the final concept elicitation interview.
- The most commonly reported fatigue-related symptoms were related to the subdomains of energy and weakness.
- Impacts of fatigue-related symptoms were reported across a number of functional and emotional subdomains.
- Based on the results of concept elicitation interviews, taking into account the above-mentioned criteria to generate items, a draft version of the instrument was developed, comprising 30 items across two hypothesized domains:
  - **Fatigue-related symptoms (16 items):** These items used an 11-point numeric rating scale assessing the severity of each item, with response options ranging from "Not at all" to "Extremely". This response scale was selected as it was determined to be appropriate for its intended use, is structured to contain suitable gradations in scores to adequately reflect change over time, and is a commonly used scale by patients in a clinical setting. A recall period of "the past 24 hours" was chosen because symptoms may change day to day.
  - **Impacts of fatigue-related symptoms (14 items):** These items used a 5-point Likert-type rating scale to assess the severity or frequency of each impact, with response options ranging from "No difficulty" to "Extreme difficulty", "Not at all" to "Extremely", or "Never" to "Almost all of the time". A numeric rating scale was not chosen for impacts, as patients may misinterpret numerical ratings as frequency counts. In addition, as items in the impact domain of the questionnaire assess different aspects of the patient experience (e.g., severity and frequency), including verbal prompts for each response choice in a Likert-type scale was considered to be important. A recall period of "past 7 days" was used for all impact items, as impacts may not be experienced during each day of a 1-week period.

Phase 2: Cognitive debriefing interviews with RRMS patients (n = 20)

- While patients generally found the draft instrument to be comprehensive, understandable, and relevant, several modifications were made based on the results of cognitive interviews:
  - 8 symptom items were removed, as >5 patients did not interpret these items as intended
  - The concept of weakness was revised to specify "physical weakness," and "while doing routine daily activities" was added to the stem of 8 symptom items
  - Phrasing of all impact items was revised to include specific reference to "fatigue-related symptoms".
- No modifications were made to the recall period or response options.
- Based on these modifications, the revised PRO instrument comprised a total of 22 items (8 fatigue-related symptoms, 14 impacts).
- Following these revisions, a Rasch analysis was conducted on the patient responses for the instrument during the Phase 2 cognitive interviews. Based on this analysis, an additional item was added to the instrument to ensure symptoms relevant for the severe spectrum of the disease were adequately covered, resulting in 23 items in total (9 fatigue-related symptoms, 14 impacts).

Phase 3: Content confirmation interviews (n = 5 PRMS interviews, n = 5 RSPMS interviews)

- Based on the analysis of the concept elicitation portion of the content confirmation interviews, it was determined that the number of interviews conducted was sufficient to achieve conceptual saturation for all symptom concepts, and all but 2 impact concepts in PRMS patients, and all but 2 each of symptom concepts and impact concepts in RSPMS patients.
- No modifications were made to the instrument as a result of the content confirmation interviews because:
  - Concepts that did not achieve saturation and were reported by only 1–2 patients, overlapped with already-included concepts, and/or were too non-specific for inclusion in the questionnaire (e.g., unable to do anything/function physically, being in a "bad mood"); therefore, no items were added to the PRO
  - PRMS and RSPMS patients generally interpreted all instructions, items, and response options as intended, and reported the concepts to be something they typically experienced.
- The PRO instrument was named the Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS™).
- The revised FSIQ-RMS™ incorporates 1 hypothesized fatigue-related symptom subdomain comprising 9 items, and 7 hypothesized impact subdomains comprising 14 items (Figure 2).

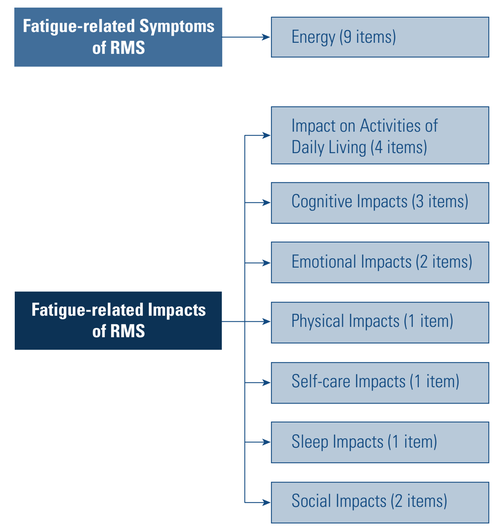

Figure 2. Conceptual framework *of the draft FSIQ-RMS™. RMS: relapsing MS.*

CONCLUSIONS

- The FSIQ-RMS™ was demonstrated to be a comprehensive measure of fatigue-related symptoms and impacts in RMS patients, and data from initial qualitative research support its content validity.
- The psychometric properties of the FSIQ-RMS™ need to be validated before the instrument can be used in clinical practice or clinical studies; this will be evaluated in a multicenter, observational trial in patients with RMS.

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