Multiple Sclerosis Working Group

Prepared for the 11th Annual PRO Consortium Workshop (April 22-23, 2020), which was cancelled due to COVID-19

PRO CONSORTIUM
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Background

Rationale of the Multiple Sclerosis (MS) Working Group (WG)

- Endpoints in MS trials have been based routinely on clinician assessments and performance-based outcome measures. It is increasingly recognized that the perspective of persons with MS should be incorporated into the evaluation of clinical benefit. Hence, a working group was formed within the PRO Consortium to explore the assessment of symptoms and functional impacts with the intent of informing PRO-based clinical trial endpoints.
- With input from FDA, the WG decided to focus on PRO measures to assess fatigue and physical function, exploring short forms from the *Patient-Reported Outcomes Measurement Information System (PROMIS®)*.

Goal of the MS WG

- To examine what should be included in measures for assessing fatigue-related and physical function-related clinical benefit in patients with all forms of MS and to evaluate the adequacy of existing PRO measures for capturing fatigue and physical function.
- To generate evidence to support the qualification of MS-specific PRO measures of fatigue and physical function; two PROMIS short forms were identified as potentially appropriate.

Concept of Interest

- Fatigue severity
- Limitations in physical function

Target Population

- Patients 18 years and older with all forms of MS

Targeted Labeling Language

- Patients treated with [*Drug X*] reported an improvement of fatigue if limited by fatigue at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed deterioration/worsening of fatigue if limited by fatigue at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed onset of fatigue if not limited in fatigue at the start of the trial.
- Patients treated with [*Drug X*] reported an improvement in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed deterioration/worsening in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported delayed onset of limitations in physical function if not limited in physical function at the start of trial.

Milestones

Milestone	Target Date	Completed Date
Letter of Intent submission to FDA		DEC 2016
Received FDA feedback on LOI; request to submit Initial Briefing Package		JUN 2017
Initial Briefing Package submission for *PROMIS FatigueMS—8a* to FDA		OCT 2019
Received feedback on Initial Briefing Package from FDA		FEB 2020
Qualification Plan submission for *PROMIS FatigueMS—8a* to FDA	2020 Q3	
Qualification Plan submission for *PROMIS PFMS—15a* to FDA	TBD	
Full Qualification Package submission for *PROMIS FatigueMS—8a* to FDA	TBD	
Full Qualification Package submission for *PROMIS PFMS—15a* to FDA	TBD	

Highlights

Example Endpoint Model for Treatment of MS

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Annualized relapse rates or confirmed disability progression (EDSS)	ClinRO
Secondary	Reduction or delayed worsening of fatigue severity	PRO
	Improvement or delayed worsening of physical function	PRO
	Clinician-reported (ClinRO) measure or a combination of performance-based outcome (PerfO) measures (e.g., walking speed, cognitive function, visual acuity, upper extremity function)	ClinRO or PerfO

Hypothesized Conceptual Framework for fatigue, based on the *PROMIS Short Form v1.0—Fatigue-Multiple Sclerosis 8a* (*PROMIS FatigueMS—8a*)

Fatigue Severity

- How often did you feel tired even when you had not done anything?
- How often did you have to push yourself to get things done because of your fatigue?
- How often did you have trouble finishing things because of your fatigue?
- To what degree did your fatigue interfere with your physical functioning?
- How often did you find yourself getting tired easily?
- How often were you too tired to think clearly?
- How often were you too tired to enjoy life?
- How often did your fatigue interfere with your social activities?

Hypothesized Conceptual Framework for physical function, based on the *PROMIS Short Form v2.1—Physical Function-Multiple Sclerosis 15a* (*PROMIS PFMS—15a*)

Physical Function Difficulty or Limitations

- …carry a laundry basket up a flight of stairs?
- …stand without losing your balance for several minutes?
- …get up from the floor from lying on your back without help?
- …hold a plate full of food?
- …dress yourself, including tying shoelaces and buttoning your clothes?
- …run errands and shop?
- …push open a heavy door?
- …exercise hard for half an hour?
- …walk with a heavy backpack (about 10lbs/5kgs) for 20 minutes?
- Does your health now limit you in hiking a couple of miles (3km) on uneven surfaces, including hills?
- Does your health now limit you in climbing several flights of stairs?
- Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?
- Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?
- How much DIFFICULTY do you currently have walking on uneven surfaces (e.g., grass, dirt road or sidewalk)?
- How much DIFFICULTY do you currently have standing up from a low, soft couch?

Highlights Continued

Existing Measures Proposed for Qualification

Measure – *PROMIS FatigueMS—8a*	Measure – *PROMIS PFMS—15a*
Number of Items: 8 **Recall Period**: Past 7 days **Response Options**: 5-level verbal rating scale assessing frequency or interference **Symptom Attribute**: Frequency or interference as a measure of severity **Data Collection Mode**: Paper or electronic	**Number of Items**: 15 **Recall Period**: None **Response Options**: 5-level verbal rating scale assessing difficulty or degree of limitations **Attribute**: Difficulty or limitations **Data Collection Mode**: Paper or electronic

Working Group Activities

Completed Activities

- Concept elicitation interviews were conducted with 14 relapsing-remitting MS (RRMS) participants and results were used to identify 48 items from the *PROMIS®* Physical Function Item Bank reflecting important impacts to upper extremity function and to mobility.
- Cognitive interviews were conducted with 43 persons with MS (26 RRMS and 17 primary progressive MS [PPMS]) to confirm relevance of physical function item concepts; of these, 29 participants (16 PPMS and 13 RRMS) were also debriefed on *PROMIS® Fatigue*$_{MS}$ items to confirm relevance of fatigue items in all patient groups. Recall with the physical function items was explored in the third round.
- Submitted the Initial Briefing Package for *PROMIS FatigueMS—8a* to FDA in October 2019
- Received grant funding to develop the *PROMIS FatigueMS—8a* Qualification Plan in September 2019

Challenges

- The majority of PRO measures developed for monitoring and evaluating outcomes in patients with MS capture distal concepts unrelated to the frequency or severity of MS symptoms, their change over time, and their impacts on functioning.
- Existing measures have a lack of conceptual focus or clarity, and were developed with a lack of input from people with MS.
- Unlike other *PROMIS®* domains, the physical function items do not have an explicit recall period since some of the activities (e.g., run errands, carry groceries, push a lawnmower) may not be done daily or even weekly. The intent is to assess the respondents' perceptions of the degree to which they are currently capable of performing the stated task or activity.

Next Steps

- Prepare and submit Qualification Plan for *PROMIS FatigueMS—8a* to FDA
- Prepare and submit Qualification Plan for *PROMIS PFMS—15a* to FDA

Working Group Participants

Company/Organization	Representatives
AbbVie	Note: AbbVie provided initial funding but is no longer participating in the WG.
EMD Serono	Paul Kamudoni, PhD (Co-Chair); Christian Henke, PhD
Roche/Genentech	Susanne Clinch, PhD
Sanofi Genzyme	Denise Bury, MPH, PhD; Keiko Higuchi, MPH, PhD
Affiliation	**Other Participants**
Accelerated Cure Project for MS	Sara Loud, MBA; Robert McBurney, PhD
National Multiple Sclerosis Society	Timothy Coetzee, PhD
Research Partner	**Research Team**
Northwestern University	David Cella, PhD; Robert Chapman, BA; Karen Kaiser, PhD; Jin-Shei Lai, PhD; Sara Shaunfield, PhD; Kayce Miller, MSc