Multiple Sclerosis Working Group

12th Annual PRO Consortium Workshop – Held Virtually on April 14-15, 2021

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

Background

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

- Endpoints in MS trials have been based 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, specifically short forms from the *Patient-Reported Outcomes Measurement Information System (PROMIS®)*.
- Endpoint measures like EDSS do not assess the full range of physical function and omit fatigue despite its prominence as a debilitating symptom of MS. Including the *PROMIS® FatigueMS—8a* and the *PROMISnq PFMS—15a* will provide a more complete understanding of the experience of individuals with MS in clinical trials.

Goal of the MS WG

- To examine what should be included in measures for assessing fatigue-related and physical function-related clinical benefit in people 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; 2 PROMIS® short forms were identified as potentially appropriate.

Concept of Interest

- Fatigue severity
- Physical function difficulty or limitations

Target Population

- Adults 18 years of age and older with any type 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 maintenance or an improvement of physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed deterioration/worsening of 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

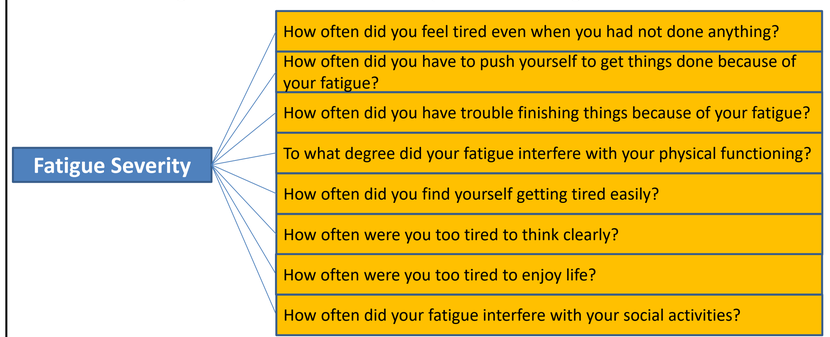
Milestone	Target Date	Completed Date
Letter of Intent submission to FDA		DEC 2016
Received FDA feedback on LOI; request to submit Initial Briefing Package		JUN 2017
Initial Briefing Package submission for *PROMIS® FatigueMS—8a* to FDA		OCT 2019
Received feedback on Initial Briefing Package from FDA		FEB 2020
Qualification Plan submission for *PROMIS® FatigueMS—8a* to FDA		AUG 2020
Reviewability memo received and response expected by May 2021		NOV 2020
Qualification Plan submission for *PROMISnq PFMS—15a* to FDA	2021 Q3	
Full Qualification Package submission for *PROMIS® FatigueMS—8a* to FDA	TBD	
Full Qualification Package submission for *PROMISnq PFMS—15a* to FDA	TBD	

Highlights

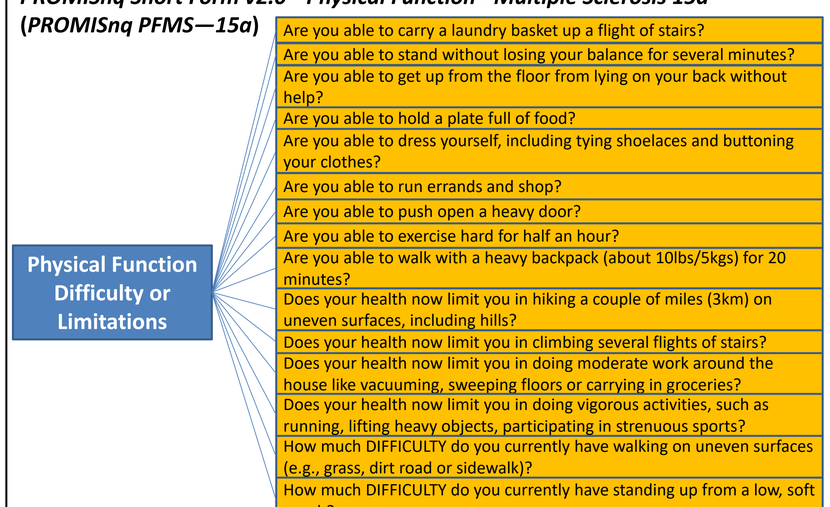
Example Endpoint Model for Treatment of MS

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 measure or a combination of performance-based outcome 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*)



Hypothesized Conceptual Framework for physical function, based on the *PROMISnq Short Form v2.0 - Physical Function - Multiple Sclerosis 15a* (*PROMISnq PFMS—15a*)



Highlights Continued

Existing Measures Proposed for Qualification

Measure – *PROMIS® FatigueMS—8a*	Measure – *PROMISnq 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 evaluate relevance of physical function item concepts and inform short form item selection; of these, 29 participants (16 PPMS and 13 RRMS) were also debriefed on *PROMIS® Fatigue$_{MS}$* items to evaluate these items in all MS types. 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
- Received grant funding to develop *PROMISnq PFMS—15a* Qualification Plan in July 2020
- Submitted the Qualification Plan for *PROMIS® FatigueMS—8a* to FDA in August 2020

Challenges

- Qualification of short forms based on a measurement system (e.g., PROMIS®) involves added requirements recently introduced by FDA to provide documentation of the original item bank calibration process and data, creating operational challenges for the MS WG.
- One possible endpoint based on physical function includes maintenance of current level of function in the treatment group compared to a control group in which meaningful decrements in physical function may be occurring.
- For the purposes of qualification, we may not be able to provide evidence to support meaningful improvement, particularly in physical function, in the current MS disease modifying treatment context, due to lack of available trial data showing improvement.

Next Steps

- Prepare and submit Qualification Plan for *PROMISnq 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