Multiple Sclerosis Working Group

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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 a reduction of fatigue if limited by fatigue at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed worsening of fatigue if limited by 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 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
Revised Qualification Plan submission for *PROMIS® FatigueMS—8a* to FDA		NOV 2021
Qualification Plan submission for *PROMISnq PFMS—15a* to FDA		NOV 2021
Reviewability memo for *PROMIS® FatigueMS—8a* received		MAR 2022
Reviewability memo for *PROMISnq PFMS—15a* received		NOV 2022
Full Qualification Package submission for *PROMIS® FatigueMS—8a* to FDA	Q3 2023	
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*)

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 *PROMISnq Short Form v2.0 - Physical Function - Multiple Sclerosis 15a* (*PROMISnq PFMS—15a*)

Physical Function Difficulty or Limitations

- Are you able to carry a laundry basket up a flight of stairs?
- Are you able to stand without losing your balance for several minutes?
- Are you able to get up from the floor from lying on your back without help?
- Are you able to hold a plate full of food?
- Are you able to dress yourself, including tying shoelaces and buttoning your clothes?
- Are you able to run errands and shop?
- Are you able to push open a heavy door?
- Are you able to exercise hard for half an hour?
- Are you able to 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 – *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 participants (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.
- Received grant funding to develop the *PROMIS® FatigueMS—8a* QP in September 2019
- Submitted the Initial Briefing Package for *PROMIS® FatigueMS—8a* to FDA in October 2019
- Received grant funding to develop the *PROMISnq PFMS—15a* QP in July 2020
- Submitted the QP for *PROMIS® FatigueMS—8a* to FDA in August 2020; submitted revised QPs for *PROMIS® FatigueMS—8a* to FDA in May 2021 and November 2021
- *PROMIS® FatigueMS—8a* QP accepted on September 6, 2022
- Submitted the QP for *PROMISnq PFMS—15a* in November 2021; reviewability assessment memo received on November 14, 2022, and under FDA review
- Received grant funding to develop the *PROMIS® FatigueMS—8a* FQP in September 2022

Challenges

- Qualification of short forms based on a measurement system (e.g., PROMIS®) involves added requirements by FDA to provide detailed original item bank calibration process and data.
- FDA's concern that impact of missing data on score reliability may differ based on which item is missing with item response theory scoring was considered a reviewability issue and required additional missing data simulation scenarios to be added to the QPs.
- Under the current MS disease modifying treatment landscape, for the purposes of the qualification, there is a lack of trial data to provide additional evidence supporting meaningful interpretation.

Next Steps

- Prepare and submit Full Qualification Package for each measure to FDA

Working Group Participants

Company/Organization	Representatives
EMD Serono	Paul Kamudoni, PhD (Co-Chair); Christian Henke, PhD
Roche/Genentech	Susanne Clinch, PhD; Evan Davies, MSc
Sanofi Genzyme	Keiko Higuchi, MPH, PhD; Natalia Hawken, PhD; Benoit Arnould, PhD; Charles Minor, MS, MBA
Affiliation	**Other Participants**
Accelerated Cure Project for MS	Sara Loud, MBA; Robert McBurney, PhD
National Multiple Sclerosis Society	Timothy Coetzee, PhD; Kathy Zackowski, PhD, OTR
Research Partner	**Research Team**
Northwestern University	David Cella, PhD; Karen Kaiser, PhD; Jin-Shei Lai, PhD, OTR; Sara Shaunfield, PhD; Kayce Plymill, MSc