# Multiple Sclerosis Working Group

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PRO CONSORTIUM CRITICAL PATH INSTITUTE

## 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®)*. The initial focus of the WG will be on assessment of fatigue.
- Because of concerns expressed by FDA regarding how recall is approached in the *PROMIS®* Physical Function item bank, the WG is placing the work associated with the assessment of physical function on hold until the recall issue can be resolved.

### Goal of the MS WG

- To examine what should be included in a measure for assessing fatigue-related clinical benefit in patients with all forms of MS and to evaluate the adequacy of existing PRO measures for capturing important fatigue symptoms. If adequate measures are found, generate evidence to support them; if no adequate measures are found, modify an existing measure or develop a new measure.

### Concept of Interest

- Severity of fatigue symptoms and experience

### 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.

## Milestones

| Milestone | Target Date | Completed Date |
|---|---|---|
| Project Kick-off: Phase 1 | | SEP 2015 |
| Qualitative research report (targeted literature review) | | JAN 2016 |
| Instrument review (targeted literature review) | | FEB 2016 |
| Instrument Review Report and Recommendations for Next Steps | | MAR 2016 |
| Project Kick-off: Phase 2 | | AUG 2016 |
| Submit Letter of Intent | | DEC 2016 |
| Receive FDA feedback to Letter of Intent; adjust focus of work to all forms of MS and to measures of physical function and fatigue | | JUN 2017 |
| Submit Initial Briefing Package for fatigue measure to FDA | Q4 2019 | |
| Submit Qualification Plan (QP) for fatigue measure to FDA | TBD | |
| Submit Full Qualification Package for fatigue measure to FDA | TBD | |

## Highlights

### Example Endpoint Model for Treatment of MS

| Endpoint Hierarchy | Endpoint Concept(s) | Endpoint Type |
|---|---|---|
| Primary | Clinician-reported or a combination of performance-based outcome measures (e.g., walking speed, cognitive function, visual acuity, upper extremity function) | ClinRO or PerfO |
| | Clinician-assessed functional disability and relapse | ClinRO |
| Secondary | Reduction in (or delayed worsening of) fatigue severity | PRO (*PROMIS® Fatigue*$_{MS}$) |

### Hypothesized Conceptual Framework for fatigue symptoms, based on the *PROMIS® Fatigue*$_{MS}$

**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?

### Existing Measure Proposed for Qualification

The MS WG is proposing the qualification of an existing measure to assess fatigue as presented in the conceptual framework above:

- *Patient-Reported Outcomes Measurement Information System (PROMIS®) Fatigue Short Form for Multiple Sclerosis* (provisionally named *PROMIS® Fatigue*$_{MS}$)

The item bank from which the measure was derived was developed through major initiatives funded by the National Institutes of Health (NIH).

### Measure - *PROMIS® Fatigue*$_{MS}$

**Core Items**: 8 items
**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

## 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 for confirmation to evaluate relevance of fatigue in all patient groups. Recall with the physical function items was explored in the third round.

### Unique Issues for the Working Group

- Many PRO measures are used to assess MS symptoms and function but few have the content coverage and/or the qualitative and quantitative evidence required to support a submission for qualification.
- The majority of PRO measures developed for monitoring and evaluation of 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.
- 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.
- Concerns have been raised about the lack of a specific recall period as well as the potential unintended consequences of adding a 7-day recall to the physical function items.
- The WG will proceed with qualification activity associated with the *PROMIS® Fatigue Short Form for MS* (*PROMIS® Fatigue*$_{MS}$) and then reassess work needed to resolve the recall period issue in order to move a *PROMIS®* Physical Function Short Form forward for qualification.

### Next Steps

- Prepare and submit the Initial Briefing Package for *PROMIS® Fatigue* $_{MS}$
- Assess whether to move a *PROMIS®* Physical Function Short Form forward for qualification

## Working Group Participants

| Company/Organization | Representatives |
|---|---|
| AbbVie | Note: AbbVie provided initial funding but is no longer participating in the WG. |
| Merck KGaA | Christian Henke; Paul Kamudoni, PhD |
| Roche/Genentech | Susanne Clinch, PhD |
| Sanofi Genzyme | Lobat Hashemi, ScD; Denise Bury, MPH, PhD |
| **Other Participants** | **Affiliation** |
| Sara Loud, MBA<br>Robert McBurney, PhD | Accelerated Cure Project for MS |
| **Research Partner** | **Research Team** |
| Northwestern University | David Cella, PhD; Karen Kaiser, PhD; Sara Shaunfield, PhD; Robert Chapman, BA |