Multiple Sclerosis Working Group

Presented at the Ninth Annual PRO Consortium Workshop – Silver Spring, MD – April 25-26, 2018

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

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

- Endpoints in MS trials have been routinely 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 treatment 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.

Goal of the MS WG

- To examine what should be included in measures for assessing physical function and fatigue-related treatment benefit in patients with all forms of MS and to evaluate the adequacy of existing PRO measures for capturing important fatigue symptoms and physical function in MS. 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.

Targeted Labeling Language

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

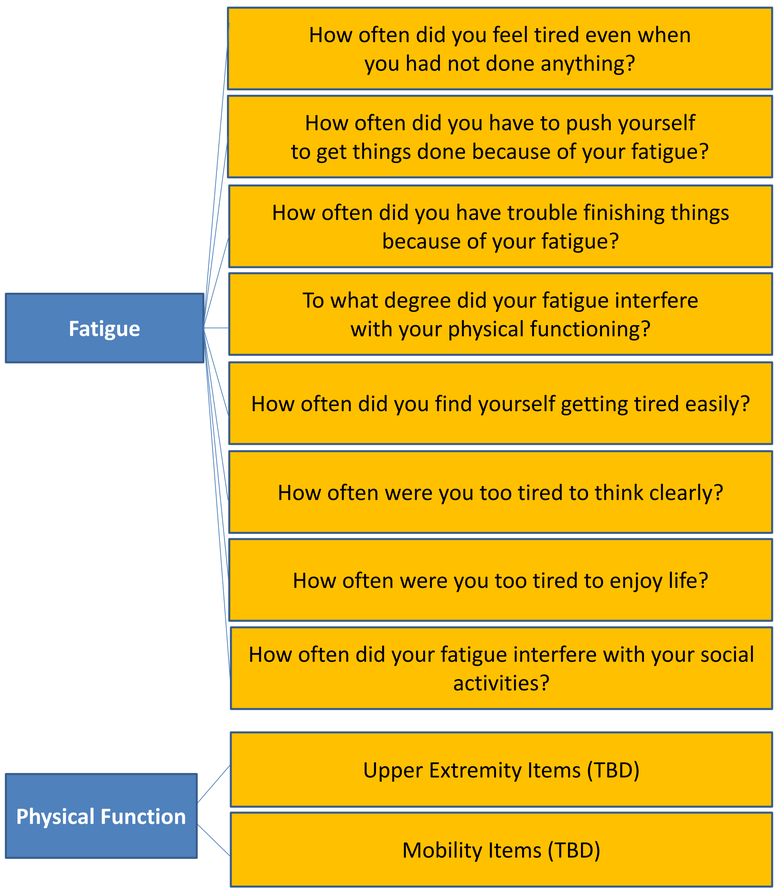
Milestone	Target Date	Completed Date
Project Kick-off: Phase 1		SEP 2015
Qualitative research and report (targeted literature review)		JAN 2016
Instrument review (targeted literature review)		FEB 2016
Instrument Review Report and Recommendations for Next Steps		MAR 2016
Decide on next steps: de novo, modification of existing or using elements of existing instruments for new instrument		MAY 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 Packages to FDA	2019Q1	
Submit Qualification Plans (QP) to FDA	TBD	
Submit Qualification Briefing Packages to FDA for exploratory use	TBD	

Highlights

Target Population

- Patients 18 years and older with all forms of MS

Hypothesized Conceptual Framework



Existing Measures Proposed for Qualification

The MS WG is proposing the qualification of two existing measures to assess fatigue and physical function as presented in the conceptual frameworks above:

- *Patient-Reported Outcomes Measurement Information System (PROMIS®) Fatigue Short Form for Multiple Sclerosis* (*PROMIS®-Fatigue*$_{MS}$)
- *PROMIS®* Physical Function Short Form (to be derived from the *PROMIS®* item bank)

The item banks from which the measures were/will be derived were developed through major initiatives funded by the National Institutes of Health (NIH).

Working Group Updates

Completed Activities

- Qualification of a symptom measure is no longer being pursued due to symptom heterogeneity and variability but a PRO measure for symptom assessment is being proposed for use alongside measures of fatigue and physical function for two reasons:
  - Consistent with FDA's efforts to encourage patient-focused drug development
  - Systematic symptom assessment in clinical trials can inform the interpretation and understanding of the functional impact reported.
- Concept elicitation interviews have been conducted with 14 relapsing-remitting MS patients and results used to identify 48 items from the *PROMIS®* Physical Function item bank reflecting important impacts to upper extremity function and to mobility.

Unique Issues for the Working Group

- Many measures are currently being used for MS patients but few have the content coverage and/or the qualitative and quantitative research 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.
- Other than for self-reported ambulatory disability (based on the 12-item Multiple Sclerosis Walking Scale [MSWS-12]) in the AMPYRA label, the lack of PRO-based labeling claims suggests a gap in the availability of suitable PRO measures for use in assessing treatment benefit in MS trials.

Next Steps

- Conduct cognitive interviews with persons with MS to confirm relevance of item concepts in progressive MS and debrief physical function items for item reduction and fatigue items for confirmation in all patient groups.
- Prepare Initial Briefing Packages for *PROMIS® Fatigue* $_{MS}$ and the new *PROMIS®* Physical Function short form.

Working Group Participants

Company/Organization	Representatives
AbbVie	Xiaolan Ye, MS, PhD
Janssen	Evan Davies
Merck KGaA	Christian Henke; Paul Kamudoni, PhD
Novartis Pharmaceuticals	Nicholas Adlard, MA, MSc, MBA
Roche/Genentech	Fiona McDougall, PhD, ClinPsyD
Sanofi Genzyme	Gisoo Barnes
Contract Research Organization	**Research Team**
Northwestern University	Dave Cella, PhD; Karen Kaiser, PhD; Sara Shaunfield, PhD; Robert Chapman