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 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 of the symptoms and functional impacts of MS and to evaluate the adequacy of existing PRO measures for capturing important symptoms and functional impacts in relapsing-remitting multiple sclerosis (RRMS). 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 [Product X] reported an improvement in physical function if experiencing limitations at the start of the trial.
- Patients treated with [Product X] reported a delayed deterioration/worsening in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [Product 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 [Product X} reported an improvement in their ability to participate in social roles and activities if limited in their ability to participate in social roles and activities at the start of the trial.
- Patients treated with [Product X] reported a delayed deterioration/worsening in their ability to participate in social roles and activities if limited in their ability to participate in social roles and activities at the start of the trial.
- Patients treated with [Product X} reported a delayed onset of limitations in their ability to participate in social roles and activities if not limited in their ability to participate in social roles and activities at the start of the trial.

Milestones

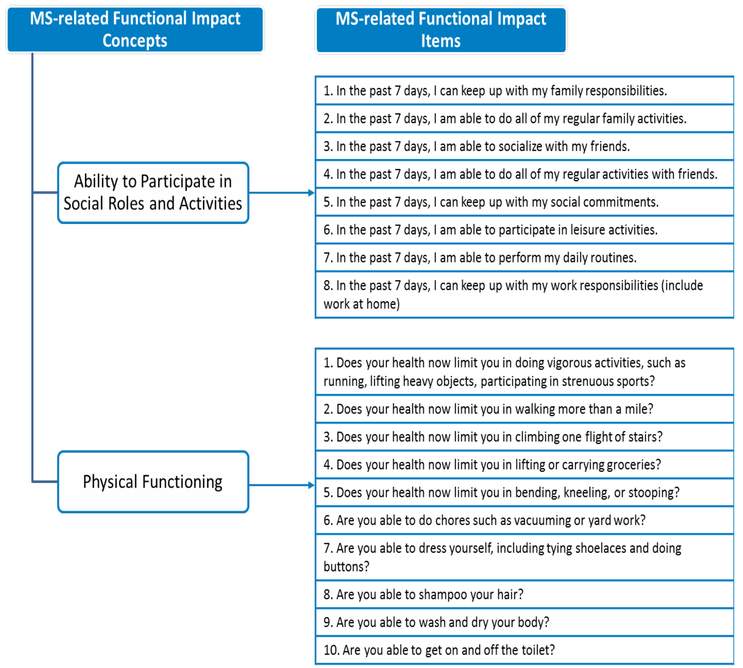
Milestone	Target Date	Completed Date
Project Kick-off: Phase 1		SEP 2015
Qualitative research and report (targeted literature review)		JAN 2016
Instrument review (targeted literature review)		FEB 2016
Instrument Review Report and Recommendations for Next Steps		MAR 2016
Item bank		MAR 2016
Decide on 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
Submit Initial Briefing Package to FDA	TBD	

Highlights

Target Population

- Patients 18 years and older with relapsing-remitting MS who are experiencing functional impacts but are ambulatory at screening as well as those who are not experiencing functional impacts at baseline but have radiological confirmation of disease progression.

Hypothesized Conceptual Framework



The conceptual framework can be broadly categorized under 'activities and participation' as defined by the International Classification of Functioning, Disability and Health (ICF):

- Participation is defined as 'involvement in a life situation' or 'the lived experience'
- Activity is defined as 'the execution of a task of action by an individual'

Existing Measures Proposed for Qualification

The MS WG is proposing the qualification of two existing measures to assess the functional impact domains presented in the conceptual frameworks above:

- Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Short Form 10a
- Quality of Life in Neurological Disorders (Neuro-QOL) Ability to Participate in Social Roles and Activities-Short Form

Both measures 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 a PRO-based assessment of functional impacts 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 functional impacts reported.

Information Dissemination

- Patel M, Crescioni M, on behalf of the Critical Path Institute's Multiple Sclerosis Working Group. Identifying Symptoms and Functional Impact Reported by Persons with Multiple Sclerosis: A Qualitative Literature Review. Student poster and podium presentation at 2016 DIA Annual Meeting, Philadelphia, Pennsylvania, June 26, 2016.

Unique Issues for the Working Group

- Symptoms and functional impacts in patients with RRMS vary between patients and can vary over time due to relapses.
- 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 regarding MS symptoms or functional impacts suggests a gap in the availability of suitable PRO measures for use in assessing treatment benefit in RRMS trials.

Next Steps

- Conduct interviews with persons with MS to confirm relevance of item concepts and debrief items included in the PROMIS Physical Function measure and Neuro-QOL Ability to Participate in Social Roles and Activities measure.
- Use a mixed methods approach to obtain preliminary information about the items and response scales in the RRMS population.
- Create an outline to guide development of psychometric analysis plans used by MS WG sponsors in future clinical trials for RRMS.

Working Group Participants

Company/Organization	Representatives
AbbVie	Xiaolan Ye, MS, PhD; Thomas Marshall
Actelion	Elke Hunsche, PhD; Evan Davies
Novartis Pharmaceuticals	Denise Simsek; Jennie Medin, MPH, PhD
Roche/Genentech	Fiona McDougall, PhD, ClinPsyD; Charlie Barr, MD, MPH
Sanofi Genzyme	Denise Bury
Contract Research Organization	**Research Team**
Outcometrix	Cheryl Coon, PhD; Jason Lundy, PhD