Cognition Working Group

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PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Cognition Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified mild cognitive impairment due to Alzheimer's disease (MCI due to AD) as a priority area.
- After extensive qualitative research, a draft PRO instrument was developed to measure complex activities of daily living and interpersonal functioning in patients with MCI due to AD.
- FDA stated concerns regarding the ability of patients with MCI due to AD to maintain sufficient cognitive insight to accurately self-report over the duration of clinical trials.
- This was confirmed during a teleconference with representatives from FDA's Study Endpoints and Labeling Development (SEALD) team and the Division of Neurology Products (DNP) held on October 7, 2014, when the FDA indicated that qualification of a PRO instrument had a low probability of success in the target population.
- FDA supported exploration by the Cognition WG of a performance outcome (PerfO) tool as a measure of functional ability in the target population; hence, the Cognition WG has revised its scope of work to focus on the evaluation of PerfO measures that could be used in patients with MCI due to AD to measure instrumental activities of daily living (IADLs). No qualified assessment tool is currently available to meet this need.

Goal of the Cognition WG

- The Cognition WG's goal is to qualify a PerfO tool to improve upon the current state of assessment of treatment benefit in clinical trials for patients with MCI due to AD. The measure will capture the patient's performance on aspects of daily functioning (i.e., IADLs) that are expected to be impacted at pre-dementia stages of AD.

Draft Labeling Language

- Patients treated with X demonstrated [XX]% improvement on performance of IADLs as compared to [XX]% improvement for patients treated with placebo.
- Patients show less decline on IADLs over time when treated with X [XX]% as compared to placebo [XX]%.

Milestones

Milestone	Expected Date	Completed Date
Content Validity Stage for PRO Measure		
Complete qualitative research for PRO measure		September 2012
Receive feedback from FDA on submitted Qualitative Research Summary Document		December 2013
Vendor selection and contracting for quantitative pilot study		July 2014
Decision by WG to redirect focus and pursue qualification of a PerfO tool based on FDA interaction		January 2015
Content Validity Stage for PerfO Tool		
Develop, refine, and finalize broad search strategy for literature review to identify up to ten PerfO tools for more in-depth evaluation		March 2015
Consult with expert panel members; complete analysis and identify PerfO tool(s) to consider for qualification		3Q2015
Submit exploratory endpoint qualification briefing document to FDA	TBD	

Content of Interest

Endpoint Model for Treatment of MCI Due to AD

Endpoint Hierarchy	Endpoint Concept(s)	Type of Endpoint
Primary	**Cognition** • Cognitive (neuropsychological) test battery	**PerfO and/or ObsRO***
	Function • Performance of instrumental activities of daily living	**PerfO**

*To be determined by each sponsor when designing its clinical trials

Target Population

- Patients 45 years of age and older
- Patients diagnosed with MCI due to AD

Hypothesized Conceptual Framework

Lawton and Brody[1]

1. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-86

Updates

- Manuscript titled "Development of a patient-reported outcome (PRO) instrument to assess complex activities of daily living and interpersonal functioning in patients with mild cognitive impairment due to suspected Alzheimer's disease: the qualitative research phase" was resubmitted to *Alzheimer's & Dementia: Journal of the Alzheimer's Association* on behalf of the Cognition WG in March 2015

- Adelphi Values performed a gap analysis on completed qualitative research, focusing on major issues identified by FDA, namely appropriate recall period and cognitive insight
- Adelphi Values' scope of work was redefined to conduct a thorough literature review of IADL PerfO tools and convene an expert panel for input
- The project formally launched in February 2015, and the following activities have been completed:
  - Developed search strategy for review of PerfO tools for assessing IADLs
  - Conducted initial review of literature to identify top 10 tools on which to perform more in-depth evaluation
  - Identified and engaged two key experts (neuropsychologists) to consult with WG on review of PerfO tools for assessing IADLs

Working Group Plans

- The draft PRO instrument will continue to be used as an exploratory endpoint in:
  - Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) prevention trial in a pre-dementia population
    - The A4 trial is a public-private partnership that includes the National Institute on Aging
  - Australian Imaging, Biomarkers and Lifestyle (AIBL) study, an observational study of MCI due to AD
- Data from these studies, using the PRO instrument in early disease, could provide evidence supporting the psychometric properties of the instrument in a pre-dementia population

Topics for Discussion

Unique issues for the working group

- Current PRO instrument will continue to be refined for potential use in very early disease (A4, AIBL)
- WG members are exploring qualification of a PerfO tool
- It is necessary to define what constitutes activities/tasks that are sufficiently reflective of IADLs

Lessons learned

- Issues remain in providing evidence to support patients' ability to reliably and validly self-report along the spectrum of MCI due to AD
- The FDA is willing to consider use of a PerfO tool as an efficacy endpoint across the spectrum of MCI due to AD

Working Group Participants

Company/Organization	Name
AbbVie	Xiaolan Ye
AstraZeneca AB	Daniel Eek
Boehringer Ingelheim	David Brill, Mark Gordon, Jeremiah Trudeau
Eisai Inc.	Anna Forsythe
Eli Lilly & Company	Scott Andrews (Co-Chair), Dan Ball
Merck Sharp & Dohme Corp	Julie Chandler(Co-Chair)
Novartis	Frederic de Reydet de Vulpillieres
Pfizer, Inc.	Alexandra Barsdorff
Genentech	Angela Rylands
Sanofi	Florence Joy

Expert Panel Members	Affiliation
Jeffrey S. Wefel, PhD, ABPP	MD Anderson Cancer Center
Robert Stern, PhD	Boston University

Contract Research Organization	Research Team
Adelphi Values	Alan Shields, Andrew Yaworsky, Funke Ojo, Iyar Mazar, Meaghan Krohe, Sasha Spite