Cognition Working Group

Prepared for the 11th Annual PRO Consortium Workshop (April 22-23, 2020), which was cancelled due to COVID-19

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Cognition Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified Stage 2/3 Alzheimer's disease (mild cognitive impairment [MCI] due to Alzheimer's disease [AD]) as a priority area for measuring AD treatment benefit.
- After extensive qualitative research, a draft PRO measure (i.e., *Interpersonal Function and Daily Activities Questionnaire v0.1* [*IFDAQ*]) was developed to assess instrumental activities of daily living (IADLs) and interpersonal functioning in patients with Stage 2/3 AD.
- FDA stated concerns regarding the ability of patients with Stage 2/3 AD to maintain sufficient cognitive insight to accurately self-report over the duration of clinical trials. Therefore, FDA indicated that qualification of a PRO instrument had a low probability of success in the target context of use.
- With FDA agreement, the Cognition WG revised its scope of work to focus on the evaluation of a performance-based outcome (PerfO) measure for use in patients with Stage 2/3 AD to measure day-to-day functioning.

Goal of the Cognition WG

- The Cognition WG's goal is to qualify a PerfO measure to improve upon the current state of assessment of clinical benefit in clinical trials for patients in clinical Stage 2 and Stage 3 of biologically-defined AD. The measure will capture the patient's performance of tasks that reflect essential aspects of day-to-day functioning.

Concept of Interest

- Day-to-day functioning based on performance of instrumental activities of daily living.

Target Population

- Patients 50 years of age and older
- Patients diagnosed with Stage 2/3 AD

Targeted Labeling Language

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

Milestones

Milestone	Target Date	Completed Date
Letter of Intent submission to FDA		MAY 2016
FDA feedback received to Letter Of Intent and approval provided to enter the *University of California San Diego Performance-based Skills Assessment* (*UPSA*) into the CDER COA DDT qualification program		OCT 2016
Initial Briefing Package submission to FDA		OCT 2019
Received IBP feedback from FDA		FEB 2020
Qualification Plan submission to FDA	TBD	
Full Qualification Package submission to FDA	TBD	

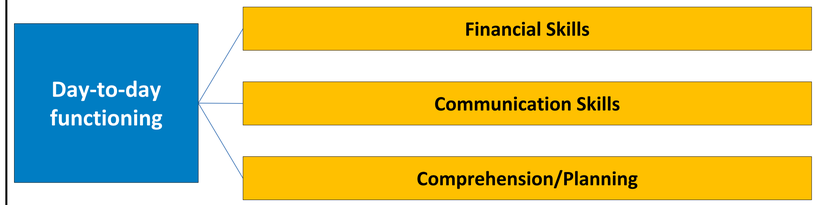
Highlights

Example Endpoint Model for Treatment of Stage 2/3 AD

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Current		
Co-Primary	**Cognition** Cognitive (neuropsychological) test battery	PerfO*
	Function Performance of instrumental activities of daily living	PerfO*
Proposed		
Primary	**Function** Performance of instrumental activities of daily living	PerfO (*UPSA-3D*)

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

Hypothesized Conceptual Framework



Existing Measure Proposed for Qualification

Measure – *University of California San Diego Performance-based Skills Assessment-Three Domain (UPSA-3D)*

Financial Skills (11 items)
- Description: Count money, make change, and demonstrate understanding of information included in a sample utility bill

Communication Skills (12 items)
- Description:
  - Telephone: Demonstrate how to use a telephone by role-playing a number of scenarios (e.g., what number to dial in case of emergency and dialing a number from memory)
  - Medical Appointment Letter: Demonstrate how to schedule a medical appointment based on information from a letter, then role-playing a number of scenarios (e.g., rescheduling the appointment, describing the letter's instructions for preparing for the appointment and the items to bring)

Comprehension/Planning (14 items)
- Description: Demonstrate comprehension of a newspaper article about the opening of a new city park (comprehension) and list seven items necessary to bring or wear in order to spend the day at the park (planning)

Administration Method: Administered by trained study personnel

Working Group Activities

Completed Activities

- Background report (including literature review and secondary statistical analysis), translatability report, and a summary report that described the process that led to the three-subscale version of the *UPSA*
- Expert panel meetings were held in March and May 2018, to address key questions regarding endpoint measures, existing gaps, and existing *UPSA* subscales
- Submitted Initial Briefing Package for the *University of California San Diego Performance-based Skills Assessment-Alzheimer's Disease* (*UPSA-AD*) to FDA
- A decision was made to change *UPSA-AD* to *USPA-3D* to reflect its three-domain structure and to avoid the implication that the measure is not applicable beyond AD

Challenges

- Several versions of the *UPSA* have been used in schizophrenia treatment trials, but there is limited empirical evidence to guide version selection for qualification of the *UPSA* in patients with Stage 2/3 AD
- A new biological definition of AD and clinical staging have emerged making the use of previous research in MCI challenging (Jack et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia* 2018;14:535-562)
- Technology has changed significantly in the past 10 years and the skills tested may not be completely relevant today, however, adaptations can be made

Next Steps

- Conduct qualitative research (e.g., pilot testing and participant interviews) with the *UPSA-3D*
- Develop quantitative pilot study protocol and quantitative analysis plan that would be the basis for the Qualification Plan
- Key areas for further evaluation of *UPSA-3D* include cultural adaptation for multinational trials, content validity confirmation, and psychometric evaluation in participants with Stage 2/3 AD

Working Group Participants

Company/Organization	Name
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Roche/Genentech	Claire Lansdall, PhD
Sanofi	Florence Joly, PharmD; Aude Roborel de Climens, PhD
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Columbia University Medical Center	Terry E. Goldberg, PhD
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Duke University Medical Center; VeraSci	Kathleen Welsh-Bohmer, PhD
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