Cognition Working Group

Presented at the 14th Annual PRO Consortium Workshop – Silver Spring, MD – April 19-20, 2023

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 retain sufficient cognitive insight to accurately self-report over the duration of clinical trials. Therefore, FDA indicated that qualification of a PRO measure 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 outcome (PerfO) measure for use in patients with Stage 2/3 AD to assess 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 treatment 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

- Persons 50 years of age and older in clinical stages 2-3 of biomarker-confirmed 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
Received FDA feedback on LOI; requested submission of Initial Briefing Package		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 (*VRFCAT-SL MCI*)

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

Hypothesized Conceptual Framework

Measure – *Virtual Reality Functional Capacity Assessment Tool – Short List Mild Cognitive Impairment* (*VRFCAT-SL MCI*)

Scenario in which tasks will be completed

Apartment kitchen
- Pick up the recipe on the counter
- Search for ingredients in your cabinets and refrigerator
- Cross off the ingredients that you already have
- Pick up the bus schedule from the counter
- Pick up the billfold on the counter
- Exit the apartment and head to the bus stop

Bus to store
- Wait for the correct bus to the grocery store and then board it when it arrives
- Add up the exact amount of bus fare and pay for the bus

Store
- Select a food aisle to begin shopping
- Continue shopping for the necessary food ingredients, and check out when finished
- Add up the exact amount for your purchase and pay for the groceries

Bus to apartment
- Wait for the correct bus and then board it when it arrives
- Add up the exact amount of bus fare and pay for the bus

Administration Method: Administered by trained study personnel on a tablet computer

Working Group Activities

Completed Activities

- Background report (including literature review and secondary statistical analysis), translatability report, and a summary report describing the process leading to the three-subscale (e.g., financial skills, communication skills, comprehension/planning) version of the *University of California San Diego Performance-based Skills Assessment (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
- After receiving support from FDA's Office of Neuroscience and Division of Clinical Outcome Assessment, the WG formally agreed in May 2021 to move forward with qualification of the *Virtual Reality Functional Capacity Assessment Tool* (*VRFCAT)* rather than the *UPSA-3D.* With the accelerated movement toward technology-enabled remote assessments, the switch to the *VRFCAT* was scientifically sound and sensible since it is a touchscreen computer-based assessment rather than requiring task completion using physical props.

Challenges

- A biological definition of AD and accompanying clinical staging have emerged (Jack et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia* 2018;14:535-562). FDA has adopted this framework and is expecting biomarker-confirmed participants in our future qualitative and quantitative research. This has been a considerable challenge in terms of the additional time and resources needed to identify sites/clinicians with potential participants with known biomarker status.

Next Steps

- Conduct qualitative research with the *VRFCAT-SL MCI* (e.g., pilot testing and participant interviews) in collaboration with Duke University Health Systems' Memory Disorders Clinic prior to the development of the Qualification Plan

Working Group Participants

Company/Organization	Name
AbbVie Inc.	Amy McLean, PhD; Anand Shewale, MS, PhD
Eli Lilly and Company	Julie Chandler, PhD (Co-Chair); Laure Delbecque, PhD
Merck Sharp & Dohme, LLC	Katy Benjamin, PhD (Co-Chair); Josephine Norquist, MS
Roche/Genentech	Claire Lansdall, PhD
Sanofi	Keiko Higuchi, MPH, PhD
AstraZeneca, Boehringer Ingelheim, and Novartis provided initial funding but no longer participate in the WG	
Affiliation	**Advisory Panel Members/Other Participants**
Alzheimer's Association Early-Stage Advisory Group	Two representatives with early AD
Boston University School of Medicine	Rhoda Au, PhD
University of Miami Miller School of Medicine	Philip D. Harvey, PhD
Massachusetts General Hospital	Roos Jutten, PhD
Banner Alzheimer's Institute	Pierre Tariot, MD
Duke University Medical Center	Kathleen Welsh-Bohmer, PhD; Richard S.E. Keefe, PhD
Consulting Organization	**Research Team**
WCG Clinical Endpoint Solutions (formerly VeraSci)	William Horan, PhD; Jenna Piunti, BA; Jared Linthicum, MS