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THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Working Group: Options and Methods to Improve Cognitive and Performance Based Assessment in Clinical Trials of AD and Its Precursors 17-Feb-2015

***Goal:*** Further understand the challenges in assessing for meaningful improvement or decrement in cognition during the clinical trial of AD or its precursors, based on modelled simulations and expanding for other aspects of cognition including social cognition and metacognition. Adding aggression and agitation at the request of Working Group members.
Panel Discussion after talks: All speakers led by ***Laurie Ryan, PhD, Chief, Dementias Of Aging Branch, Program Director, Alzheimer's Disease Clinical Trials Division of Neuroscience, NIH/NIA***

***Dr. Lon S. Schneider (Professor of Psychiatry, Neurology, and Gerontology, Keck School of Medicine of USC, Los Angeles, CA)*** – Using Full AD Clinical Trials Datasets for Simulations and Modeling of Future Clinical Trials. Given the imperative to run clinical trials with fewer patients and as early a signal as possible, Schneider and colleagues investigated the effects of implementing several recently suggested changes for enrichment. They used several metadatabases including ADCS, ADNI and CAMD, spanning cognitively normal to AD, 6500 participants, 6.7% African American and 8.2% Hispanic. Simulation methodology: 1:1 allocation treatment to pbo. Used resampling method to simulate typical clin trial: 50-400/arm, 12-24 mos., 20-40% drop-outs. Constructed the treatment and pbo groups by resampling the entire metadatabase. Treatment effects were added to scores in the treatment group with effect sizes of 0.15 to 0.55. (*Schneider et al Alz & Dem, 2010*). Multiple studies were considered: post hoc ApoE, minority, biomarkers ApoE, biomarkers Aβ, age, aeverity, adaptive design – sample size reestimation. For post hoc analysis of ApoE with smaller samples, may give an incorrect target for future trials. Up to 25% of MCI trials and 37% of AD trials had greater rate of progression in ApoE4-. The majority were not statistically significant. The proportion of statistically significant results favoring ApoE4- decreased with sample size: <5% with 125 subjects /arm for AD. Consistent with a chance finding due to the size of the sample. What happens if the minority population is increased? Concerns include (1) exclusion of comorbidities common in minorities, (2) dropout and retention, (3) increased variability on outcomes. Examined this in databases with 20%-80% African Americans. African Americans had higher rates of several disorders (primarly cardiovascular and respiratory). The increased participation of African Americans had little or no impact on trial outcome; nearly identical power with larger samples. Enrichment based on biomarkers. ApoE4+ enrichment resulted in less than 3% increase in power for each simulated condition. Recruitment time and/or number of sites would increase since 60% of AD trial participants are ApoE4+. About 70% meet $A\beta_{1-42}$ cutoffs. Enrolling all participants (with possible stratification on ApoE4/$A\beta_{1-42}$) would be more effective in most trials. AD trial outcomes based on age *Schneider et al. Neurology 2015;84:1-7*. Age strongly predicts change in ADAScog and MMSE; thus the clinical interpretation of change on these scales differ depending on age. Adaptive design: Sample size reestimation: can be critical in certain circumstances depending on the patient population. For MCI: SSR at 6 mos with 100 subjects /group added 23% and 24% power for 18 and 24 mos trials. For AD: SSR at 6 mos with 100 subjects per arm added 16% power for 18 mos trials, but depends on the recruitment rates before the SSR is done. Dr. Schneider's collaborators on this are Richard E. Kennedy MD, PhD, and Gary R. Cutter, PhD, University of Alabama, Birmingham.

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***Dr. Stephanie Cosentino (Assistant Professor of Neuropsychology, Taub Institute, Columbia University, NY)*** – General cognition, social cognition, and metacognition are separable. **Social cognition** is the means by which we make sense of ourselves in relation to others and the environment in which we live; also conceived as the process that is engaged to understand or interpret the self in relation to others. Elements include emotional perception, moral reasoning, perspective taking, social knowledge. And, skills like empathy and self-monitoring, decision-making ,and behavior. A neuroanatomic substrate has been identified which involves the orbitomedial PFC, midline structures, insula, anterior temporal lobes, and this network is often right lateralized. In AD, social cognition is frequently characterized by preserved social cognition. It can remain intact into moderate stage, but a range exists, especially if measured objectively instead of by an informant. An example of a task on social cognition is the *Theory of Mind Task* where the subject is asked to differentiate between his/her own knowledge and that of another individual. Patients with early AD have trouble with this task (difference between where the viewer knows a ball has been placed versus where the person in the story would think it is.) *Alz & Dem 10 (2014) 818-826* looked at cross-sectional and longitudinal associations between general cognition, social cognition, and dependence measured with six items from the *Blessed Dementia Rating Scale*. Social cognitive symptoms measured this way look flat after 5 years, but probably reflect increase in some symptoms and decrease in others. Other objective/experimental assessments may change more linearly over time: Attribution of Intention (AD with MMSE <25 performed differently), referential discourse, moral reasoning, emotion perception. **Metacognition:** This relates to decision-making capacity. Memory awareness influences everyday decision making capacity about medication management and other everyday activities in AD. An objective metamemory task: give subject 5 fake facts. Ask people what they think they will remember. Score their prediction accuracy dyad (gamma correlation) to determine whether predictions and accuracy dyads are concordant vs. discordant. In other words, does the person adjust their predictions on accordance with their actual accuracy? The score is unrelated to age, education or MMSE; it is closely related to clinician's rating of their awareness which indicates that it captures something specific to self-monitoring.