Options and methods to improve cognitive & clinical primary endpoint assessment in clinical trials of Alzheimer's Dementia and its precursors

ISCTM Autumn Conference Workshop

Options and Methods to Improve Cognitive Assessment in Clinical Trials of AD and its Precursors

Chairs: Holly Posner, MD (Pfizer*) & Philip Harvey, PhD (University of Miami School of Medicine)

Speakers: David Loewenstein, PhD, ABPP/CN, Professor of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine

Developing More Effective Paradigms for Assessing and Monitoring Cognitive Change Across the MCI and PreMCI Spectrum

Steve Edland, PhD, Professor of Statistics and Neuroscience, UCSD

Four statistical considerations in trials on AD and its precursors

Eric Bastings, MD U.S. Food & Drug Administration, Acting Director, Division of Neurology Products, Center for Drug Evaluation and Research (CDER)

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* Dr. Posner works for Pfizer; she does not work on Alzheimer's at Pfizer and her work does not represent that of Pfizer

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Major Content Areas:

- Understand challenges when assessing meaningful improvement or decrement in cognition during a clinical trial of AD and its precursors
- Target the drug under study's mechanism of action, phase, start date, and study population of a given clinical trial and to a clinical outcome that maximizes statistical sophistication, biomarkers, and the best regulatory approach
- Specific statistical, and psychometric approaches focused on MCI or Preclinical AD
- Regulatory considerations

Overview of Issues Discussed:

COGNITIVE & FUNCTIONAL ASSESSMENT/PSYCHOMETRICS

- Treatment trials may fail if cognitive and functional outcome measures are not sensitive, ie., have sufficient granularity, range and are targeted to the deficits of the population being studied
- There are significant challenges of using traditional measures when trying to capture MCI, PreMCI, and Preclinical AD states to assess the impact of an intervention, including lack of sensitivity in terms of normative data issues, impact of ceiling effects, insufficient granularity
- Given the heterogeneity of AD phenotypes, utilizing a measure that has embedded indices may be more sensitive across the spectrum of disease and able to pick up changes
- To improve sensitivity, each person acting as their own control works better than group normative data.
- Controlled learning conditions can minimize variability by comparing an individual's performance to his or her optimal capability at baseline
- CDR sum of boxes alone may be limited due to caregiver report bias. CDR sum of boxes plus objective cognitive assessment may improve the measure.

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STATISTICAL

- A composite measure can be derived from sensitive existing measures
- Optimizing an outcome measures may be achieved through increasing relative efficiency
- Utilizing techniques such as IRT Item response theory models may be used to recalculate "latent traits" that are relevant to measure or reduce ceiling effects and capture change
- Statistical techniques and understanding variability may maximize efficiency by reducing recruitment demands. Being more thoughtful about statistics improves efficiency.
- Composite outcome measures may result in a more accurate appraisal of outcome in a treatment trial.
- Designing a composite requires finding the optimal methods including using the weighted average (optimal weight) and design term. More focus on the design term is needed.
- When using data to power a trial (ADNI vs. ADCS data), consider the differences between the powering data and the your new study. The populations will have differences and caution should be used when designing the trials if considering using composites derived from epidemiologic populations such as ADNI. If a clinical trial dataset is used, consider the environment in terms of likely concomitant medications, diagnostic differences, and eligibility criteria compared to the trial you are designing

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REGULATORY

- Primary efficacy endpoint must be related to meaningful treatment benefit either directly (how a patient feels, functions or survives) or indirectly (cognitive scale in AD) that provides evidence of the relationship between the indirect relationship and how the patient feels or functions.
- Single primary outcome measure , that combines cognition and function, such as the CDR-SB, is considered acceptable in MCI. For an approval a study would need to show benefit in both components.
- A cognitive effect alone is not sufficient in MCI. In preclinical AD it can be the basis for an accelerated approval with a subsequent post approval study showing functional benefit. To gain this, there is the expectation that the drug is disease modifying and that the benefitwould grow over time. The post marketing study would be an extension of the original approval and the subjects would remain blinded

There were also questions and answers that were discussed and will be posted on the ISCTM website. These are summarized here:

- Composite endpoints must demonstrate contribution of both cognitive and functional elements in overall endpoint effect
- The use of imaging and biomarkers alone will not be considered as valid surrogate outcome measures until the relationship between these and the clinical outcomes is well understood and found to be reliable
- For the purpose of use as part of a primary endpoint in a trial reviewed by DNP, as long as a (neuropsychological) scale measures clinically important elements, revalidation may not be required; specifics should be discussed with the division.

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