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Workshop: Options and methods to improve cognitive assessment in clinical trials of AD and its precursors

Overview of issues

Holly B. Posner, MD, MS

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*Dr. Posner's disclosures: works at Pfizer in Clinical R&D in a area unrelated to Alzheimer's Disease. Not speaking on behalf of Pfizer.

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Goals

- Further understand the challenges in assessing for meaningful improvement or decrement in cognition during the 6 month to 2 year period of a typical clinical trial of AD and its precursors
- Dissect when to apply a specific statistical, psychometric and/or regulatory approach according to the phase, start date, and study population of a given clinical trial

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Regulatory Changes

- Dual primary endpoint: cognitive and functional
- Recent guidance: CDR-SB alone as a primary endpoint
- Relatively recent introduction of the endpoint qualification process

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Diagnostic changes

- New guidelines that incorporate biomarkers
- Original studies, mainly clinical criteria (and pathologic)

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Target Changes in Trials

- Both population and biological
- Taken together, clinical trial populations span a greater range of the disease from minimal cognitive or functional decline to AD
- Individual studies target a specific range of decline
- Molecular targets beyond amyloid (multipronged approach)
- Goal for the field: understand prospectively, for a given cognitive people's health economics status changes over the following few years (make better cost/benefit estimates for what is a meaningful change)

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Clinical outcome changes

- From the ADAS-cog + ADCS-ADL/CIBIC+
- To CDR-SB, Composite endpoints, Biomarkers
- And, specifically the cognitive endpoint batteries in the 3 genetic trials

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Statistical Sophistication

- Composite endpoints (S. Hendrix)
- Item level analysis (Hobart showed that the ADAS-cog is mistargeted for milder patients (among other problems); too easy and hard to show improvement)
- Dr. Edland's talk

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Conclusion

- Best options differ by stage of the drug development program and the time / money available to develop a new endpoint.
- Need to work together as interested parties, academics, pharmaceutical company employees, NIH/NIA, FDA, Alzheimer's Association, etc, to evaluate the issues at each stage in a drug's development

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Goals and History of This Effort

Philip D. Harvey, PhD

University of Miami Miller School of Medicine

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History of this Effort

- Treatment trials have been failing in AD and it has been suggested that the outcomes measures may not be sensitive
- Outcomes measures were not necessarily developed to be used in treatment studies
- MCI and pre-MCI poses a whole new challenge

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Previous Discussions

- Can existing measures be compiled into a useful composite?
  - What are costs and benefits?
- Is a special validation procedure required?
  - Like the MATRICS initiative
- Can we clarify the boundary between performance-based and patient reported outcomes?
- Can existing performance-based functional capacity measures be used to supplement performance-based NP measures?

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Issues we have considered

- Is a downward extension from AD a valid way to think about MCI or pre-MCI?
  - Are the tests just too easy or are there impairments not covered in previous instruments
- Are there critical aspects of MCI that are not covered by existing measures?
- Are there psychometric strategies other than composites that can be used to boost signal?