Sensitive Outcome Measures for Clinical Trials in Earlier Alzheimer's Disease

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Rationale for more sensitive endpoints in AD

- Current AD trials require co-primary endpoints of cognition and function (or global measure).
- ADAS-Cog: the standard cognitive endpoint instrument; developed for moderate/severe AD; but insensitive in early disease due to ceiling effects.
- Clinical trials in progress or en route for disease-modifying agents are targeting early disease.
- No current standard for the co-primary functional global score for AD or MCI.
- FDA amenable to revisiting endpoints, even single composite endpoints for MCI trials.

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ADAS-Cog & CDR-SB Subscales

ADAS-Cog Subscales:

Q1: Word Recall

Q4: Delayed Word Recall (In ADAS-13)

Q7: Orientation

Q8: Word Recognition

Q9: Recall Instructions

Q14: Number Cancellation (In ADAS-13)

Q3: Construction

Q6: Ideational Praxis

Q2: Commands

Q5: Naming

Q10: Spoken Language

Q11: Word Finding

Q12: Comprehension

CDR Sum of Boxes Subscales:

Cognition:

Memory

Orientation

Judgement.

Function:

Home & Hobbies

Personal Care

Community Affairs.

Standardized Changes from Baseline for Certain Subscales & Composites

Scale	Mean 2-Yr Change	SD (2-Yr Change)	2-Yr Change Standardized
Q1 (Word Recall)	0.41	0.76	0.54
Q4 (Delayed Word Recall)	0.32	0.68	0.47
Q7 (Orientation)	0.55	1.06	0.51
ADASCog 11	0.48	0.89	0.54
ADASCog 13	0.47	0.76	0.62
CDRCog (Memory, Orientation, Judgement)	0.76	0.97	0.78
TriAD (Q1, Q4, Q7, CDRCog)	0.64	0.76	0.85

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Development of a Sensitive Endpoint for a Specific Disease Stage

Our Approach:

Selection of Composite Components

Performance Evaluation of Composites

Validation of Component and Composite Scales

Other Approaches:

Different Selection Criteria

Different Evaluation Criteria.

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Conclusions

- We can develop more sensitive outcome measures for MCI from existing instruments e.g. TriAD = 3 ADAS subscales

  + 3 CDR subscales.

  - Greatly improved effect size over ADAS11 and therefore power to enable MCI trials.
  - Interrogates several domains affected in MCI: Memory, Orientation and Executive Function.
  - Relies on both quantitative and clinical assessments. Thus mitigates against poor performance of either measure in a trial (eg. Learning effects, reliance on clinical expertise of rater).
- Even more sensitive outcome measures for MCI by combining with functional measures, with additional advantage of replacing separate co-primaries.
- Greatest gains can be achieved by combining cognitive-functional composites with biomarker-based enrichment strategies.

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