Clinical Outcome Measures - An Industry Perspective

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Declaration of Conflicts of Interest

Veronika Logovinsky is an employee of Eisai Inc.

The presentation is being made on behalf of the EFPIA working group and does not represent the views of Eisai Inc.

Key considerations

- How can clinical progression and treatment response be measured in Preclinical and Prodromal AD?
  - Preclinical AD represents asymptomatic stages with or without memory complaints and *emerging* episodic memory and executive function deficits
  - Prodromal AD represents pre-dementia stage characterized *predominantly* by cognitive deficits and *emerging* functional impairment with disease progression
- How can clinical meaningfulness of treatment effects be established in in Prodromal AD?
  - In Prodromal AD effect on cognition is predominant while effect on function is difficult to measure
- How can clinical meaningfulness of treatment effects be established in Preclinical AD?
  - In Preclinical AD only effect on cognition is likely measurable
  - Prevention trials will be large and extremely long to show reduction in incidence of disease related cognitive deficits
  - Lack of established surrogate biomarkers precludes alternatives to clinical outcome measures for all pre-dementia stages (Preclinical and Prodromal AD)

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Difficult to Measure Change in Prodromal and Preclinical AD

Preclinical → Prodromal → Dementia

Preclinical	Prodromal	Dementia
Memory complaints	*Cognitive Impairment*	*Cognitive, Functional & Behavioral deficits*
Preclinical	**aMCI / Prodromal AD**	**Mild** **Moderate** **Severe**
No apparent symptoms	*Emerging functional impairment*	

- **Prodromal AD: current instruments may**
  - Have suboptimal sensitivity to clinical progression and treatment
  - Have challenges measuring subtle functional impairments
  - Have been inconsistently used in Prodromal AD clinical trials and lack historical data
- **Preclinical AD: Episodic Memory and Executive Functioning deficits emerge**
  - No measures established in interventional trials
  - Wealth of alternative measures that lack trial data
- **Prevention trials will be large and extremely long to show reduction in disease incidence**
  - Need very high sensitivity to emerging clinical symptoms

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Different Outcomes: Performance-Based Outcome Measures

Established / De Novo Psychometrically-Derived Performance-Based Outcome Measures

- Available measures, but have not been utilized in interventional trials
- Designed to meet established reliability and validity standards
  - Reliability – Test-retest; Alternative-Form; Inter-rater reliability
  - Validity – Construct; Criterion; Content; Predictive; Face (Ecological); Convergent; and Discriminant
- Aim to focus on cognitive domains affected early in disease
  - Episodic memory and timed Executive Functioning

- *Drawbacks - lack of systematically collected trial data needed for power analyses, modeling purposes and understanding of treatment response*
- *Need to be included in future trials → will take years before "established"*

Different Outcomes: Patient-Reported Outcome (PRO) Measures

- PRO Scales ~ De Novo Scales (no established PRO scales in Prodromal AD/MCI or AD dementia)

- The Cognition Working Group of the Critical Path Institute's Patient-Reported Outcome Consortium seeks to develop a PRO instrument to be qualified by the FDA as an efficacy endpoint in clinical trials of patients with MCI due to AD
  - capture the patient's perspective on specific aspects of functioning
  - contribute to the description of disease progression and the measurement of treatment effects

- Current status of C-Path PRO: qualitative research phase

Main challenges in developing PRO measures for Prodromal AD/MCI patients

- Specification of a recall period for the instrument
  - Frequency of individual activities highly variable

- Variability of engagement in individual activities

- Preservation of insight (critical in ensuring the reliability and validity of patient reports) in population with progressing cognitive deficits:

  - Crucial to understand where along continuum of progression to AD dementia patients lose ability to accurately self-report

  - There is uncertainty about method(s) for determining adequacy of patient insight

New Outcome Measures in Preclinical and Prodromal AD

- **Improvement of established scales – focus on sensitivity**
  - Also aim to increase responsiveness to therapy
  - Preserve clinical meaningfulness
- **De Novo Scales –**
  - **focus on theoretical constructs**
    - Foundation in psychometric principles (e.g., construct validity)
    - Based on assumptions on clinical meaningfulness (e.g. face validity)
  - *Drawback - lack of historical data - resource-intensive & time-consuming*
  - **focus on standardization and ease of use**
    - Computerized tests – emphasis on sensitivity and potential for remote use
  - *Drawback - lack of historical data; unclear support for clinical meaningfulness*
- **All new outcome scales should be subject to standardized validation process with clearly specified requirements**
- **It is essential to standardize characteristics of target population when comparing performance of new outcomes across different trials with data sharing being key to this process**

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Issues Around Clinical Meaningfulness in Preclinical and Prodromal AD

At early stages AD is primarily disease of cognition:

- cognitive decline precedes and predicts functional decline (Zahodne et al. 2013; Liu-Seifert et al. 2014a)
- effect on cognition should be important consideration in assessment of clinical meaningfulness

Additional information can be combined with results on specific clinical outcome in support of clinical meaningfulness:

- Treatments aimed at the underlying pathophysiology of AD should slow clinical decline and the effect should grow over time
  - This may be demonstrated by an increasing magnitude of effect, point difference over time, or percent reduction in decline
- Biomarkers of underlying AD pathology may be clinically meaningful
- Time-to-event or responder analyses, have been suggested as conceptually appealing measures of clinically meaningfulness
  - associated with practical difficulties, such as dichotomizing 2 disease stages (pre-dementia vs. dementia) that exist along a continuum (FDA 2013) or defining new, standardized and agreed upon events that signal clinical progression

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Efforts to Develop Clinical Measures for Prodromal AD

- **Tools developed by industry & academia for early stage AD**
  - Use existing data sets and established measures
  - ***Validity and clinical meaningfulness "borrowed" by using established scales for dementia AD***
  - Select elements responsive to clinical progression in this disease stage
    - Emphasizing items sensitive in Prodromal AD
    - ADAS-Cog alone or additive scales by combining ADAS-Cog with items from other instruments (CDR-SB, MMSE, FAQ etc.)
  - Modifications to increase sensitivity to decline and treatment effect
    - Improved weighting provides further optimization

- **Results - <u>Composite Clinical Endpoint</u> with weighted items from established scales, e.g. ADAS-Cog, CDR-SB and MMSE**
  - These composites converge on selected items

Progression of Composites for Prodromal AD

1 - Individual Efforts

2008 – onwards

Composite & Cognition Scores developed by Industry & Academia

2 - Start of cooperation

2009 – 2013

ADNI PPSB (Industry Group) ADAS-Cog Plus Working Group

3 - Harmonization of Efforts

2012 – onwards

ADNI PPSB Data Mining Session & Clinical End Points Working Group

4 - Regulatory Qualification

2013 – 2016

CAMD (C-Path Institute): pCOA Project

1. Data analyses on candidates selected in PPSB CEWG
2. Submission Letter of Intent to FDA and EMA – Stage 1
3. Submission of Qualification request to FDA and EMA – Stage 2
4. Aim for approval of new Instrument (as primary EP)……

Emerging Outcomes for Preclinical AD

Developing Clinical Outcome Tools

- De novo scales – highly sensitive to very early symptoms
- Computerized tests – lack clinical meaningfulness
- Rely on ongoing observational studies to validate measures

- *Drawbacks - lack of historical data; lack of trial data, no link to clinical meaningfulness data*
- *Years before "established"*

Biomarkers of Pathophysiological Progression

- Surrogates for clinical measures

- *Drawbacks – lack of strong candidate biomarkers as outcome measures, less so for early stage of disease, no correlation established between clinical outcome and biomarkers data in trials*

Examples of Measures Used in Preclinical AD

- **AD Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC)**
  - Drug trial in at-risk (amyloid positive) cognitively normal subjects (A4 trial)
  - Primary Outcome measure is a cognitive composite based largely on theoretical considerations
- **Alzheimer's Prevention Initiative (API) & Arizona Alzheimer's Consortium includes**
  - Natural progression study & intervention trial in extended family in Colombia with PS mutation
  - ApoE4 homozygotes trial in cognitively healthy older adults
  - Methodological approach similar to those used for clinical composites in Prodromal AD - weighted combination of measures of cognitive decline over time identified via annualized mean-to-standard-deviation ratios (MSDR) analysis (data driven approach)
- **Dominantly Inherited Alzheimer Network (DIAN)**
  - Natural progression study & intervention trial in adult children to parents with dominantly inherited AD
  - Cognitive composite is under development with several approaches tested (composite similar to ADCS-PACC; other theoretically based composites)

Regulatory Challenges

- Unclear pathway toward gaining acceptance for data-driven tools, optimized for Pre-dementia/Prodromal AD

- Unclear what data are required for establishing validation of an outcome measure

- Concerns that
  - the key symptom in this stage, cognition, would be the only driver treatment effect
  - outcome measure continues to develop as new data emerges
  - sensitivity overshadows clinical meaningfulness

- Unclear requirements for data from retrospective and prospective studies for acceptability of newly developed tools

Key regulatory questions (1/3)

- Question 1: How late in AD continuum is cognitive treatment benefit (alone or in combination with biomarkers of disease pathology) sufficient to establish efficacy?

- *EFPIA proposes that*
  - *Cognitive treatment benefit should be sufficient to establish efficacy for registration for Preclinical AD*
  - *In Preclinical AD large trials of 10+ years in duration would be required to show reduction in disease incidence; additional data obtained outside of registration trials (e.g. data from relevant observational studies) should be allowed to supplement efficacy data*

Key regulatory questions (2/3)

- Question 2: What balance of cognitive / functional effects is acceptable in Prodromal AD?

- *EFPIA believes that*
  - *Prodromal AD is characterized predominantly by cognitive deficits and subtle emerging functional impairment with disease progression*
  - *Desirable approach is to consider outcome tools for Prodromal AD, including the newly developed composites, as reflecting both cognition and function without attempting to map separate contributions of cognitive vs. functional domains, so that statistically significant treatment effect as captured by the entire tool is acceptable*

Key regulatory questions (3/3)

- Question 3: EMA “Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer´s disease and other dementias” (released on 23 October 2014) states that “…, the recently introduced ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC) or Alzheimer’s prevention initiative composite test score (Langbaum et al. 2014) might be examples of suitable tools…” in Prodromal AD.

  Is it correctly understood that a cognitive scale could be used as the single primary endpoint in Prodromal AD?

- *EFPIA is asking to clarify:*
  - *What specific data and analyses are required to validate new composite tools for use as primary outcome measures?*

Back-Up Slides

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- **AD Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC)**

  - Drug trial in at-risk (amyloid positive) cognitively normal subjects (A4 trial)
  - Primary Outcome measure is a cognitive composite based largely on theoretical considerations
  - Cognitive composite of 4 measures sensitive to decline in prodromal and mild AD dementia - sufficient range to detect early decline in the pre-symptomatic AD
    - Total Recall score from the Free and Cued Selective Reminding Test (FCSRT)
    - Delayed Recall score on the Logical Memory IIa subtest from the Wechsler Memory Scale
    - Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale–Revised
    - MMSE total score

Examples of Measures Used in Preclinical AD

- **Alzheimer's Prevention Initiative (API) & Arizona Alzheimer's Consortium includes**
  - Natural progression study & intervention trial in extended family in Colombia with PS mutation
  - ApoE4 homozygotes trial in cognitively healthy older adults

- Methodological approach similar to those used for clinical composites in Prodromal AD
- Weighted combination of measures of *cognitive* decline over time identified from a battery of 19-21 cognitive tests, via annualized mean-to-standard-deviation ratios (MSDR) analysis (data driven approach)
  - Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Recall
  - CERAD Boston Naming Test (high frequency items)
  - CERAD Constructional Praxis
  - Raven's Progressive Matrices (Set A)
  - MMSE Orientation to Time

Examples of Measures Used in Pre-Symptomatic AD

- **Dominantly Inherited Alzheimer Network (DIAN)**
  - Natural progression study & intervention trial in adult children to parents with dominantly inherited AD
  - Cognitive composite is under development with several approaches tested:
    - Composite similar to ADCS-PACC with
      - word-list recall task
      - Logical Memory
      - MMSE: 5 orientation items
      - associative memory task
    - Theoretically based composites with focus on
      - episodic memory
      - executive function
      - attention
      - language

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