CAMD Annual Meeting
Predementia Clinical Outcome Assessment (pCOA) Project

Johan Luthman, DDS, PhD (Eisai)
Michael Ropacki, PhD (Janssen R&D)

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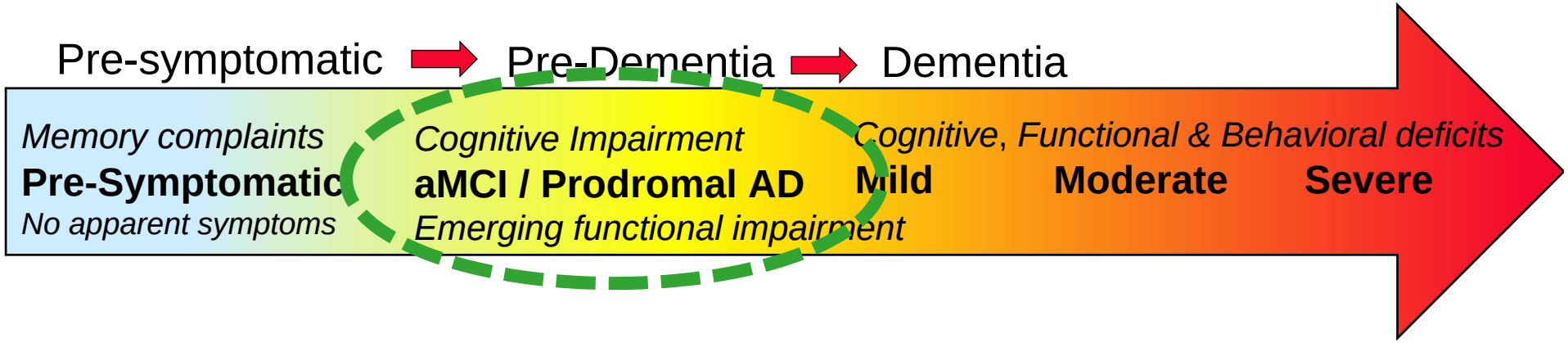
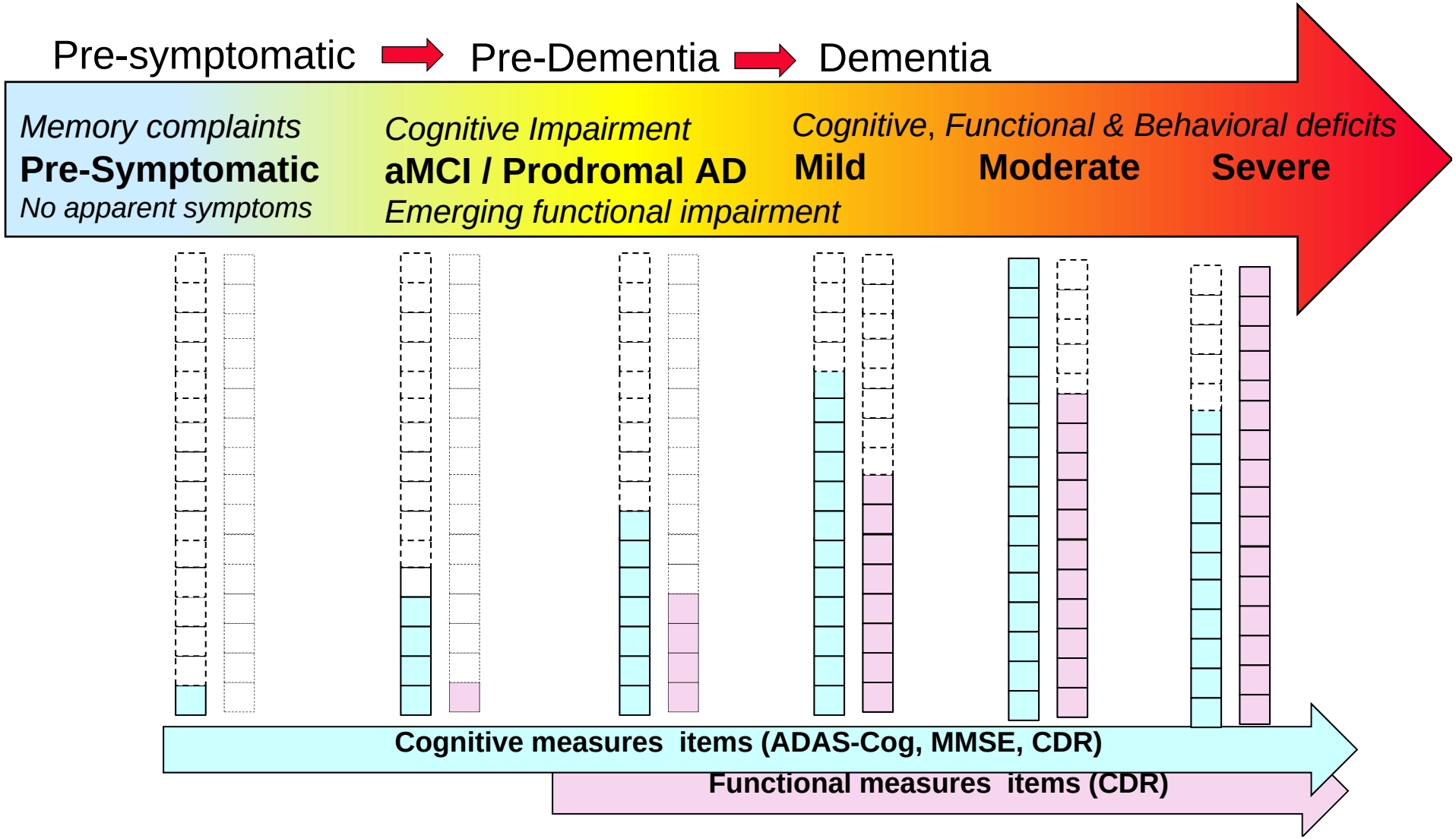
How to Measure Deficits in the "Pre-Dementia" Stages of the AD?



- Established Clinical Outcome Measures lack sensitivity & responsiveness in early stages of the disease:
  - ADAS-Cog: Ceiling effects
  - MMSE: Ceiling effects
  - CDR-SB: May not have sufficient responsiveness to treatment
  - Limited data for several tests, e.g. NTB, Computerized Cognitive tests
  - Challenges measuring functional impairment in aMCI/Prodromal AD

*Alzheimer's Disease Assessment Scale Cognitive Subscale; Clinical Dementia Rating; Mini Mental State Examination

Gradual Sensitivity of Cognitive & Functional Items of Established Measures



Different Approaches for Clinical Outcome Assessments

Clinician- or performance- Reported Outcome Measures

➢ ***Established measures – suboptimal for Pre-dementia AD***

- **Improvement of existing scales – focus on sensitivity**
  - Large available data sets
  - Preserved 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)

- **De Novo Scales - focus on standardization & easiness of use**
  - Computerized tests – emphasis on sensitivity

Patient (or Caregiver) Reported Outcome Measures

- **How patient feels/functions regarding health, condition, or disease**
  - Information directly from the patient (no assessment by physicians or others)

- **PRO Scales ~ De Novo Scales - no established PRO scales in AD**

Efforts to Improve of Existing Clinical Measures for application in Early Stage AD

Individual industry & academic efforts have proposed more sensitive and responsive measures in early stage AD

- Some measures, especially cognitive, are more sensitive (e.g. delayed word recall, orientation, word recognition)

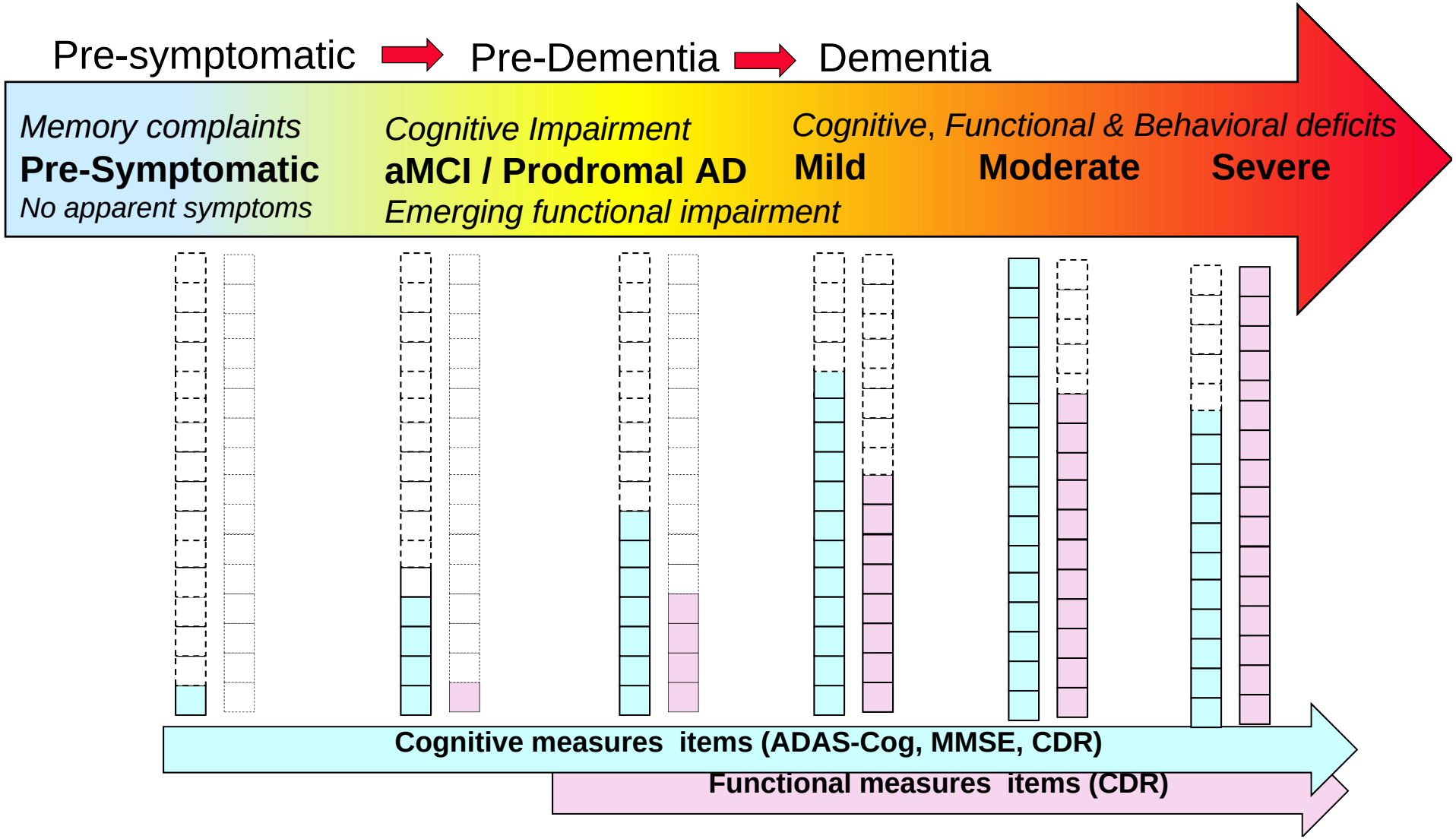
<u>Composite Clinical Endpoint</u> with items from established scales, e.g. ADAS-Cog, CDR and MMSE

Validity "borrowed" by using established, commonly used, scales

- ❑ Emphasizing cognitive measures of performance

- General approaches:
  - ➢ Improved weighting of ADAS-Cog items (multivariate modelling)
  - ➢ Additive scales by combining ADAS-Cog with items from other instruments (CDR, MMSE, FAQ etc.)
  - ➢ A combination of both approaches

Over Time Gradual Increase of Cognitive & Functional Items of Established Measures



Increase Fidelity of Responsive Items by Weighting & Deletion

Increase Fidelity of Sensitive Items Exclude Non-Responsive Items

Pre-symptomatic ➡ Pre-Dementia ➡ Dementia

Memory complaints
Pre-Symptomatic
No apparent symptoms

Cognitive Impairment
aMCI / Prodromal AD
Emerging functional impairment

Cognitive, Functional & Behavioral deficits
Mild **Moderate** **Severe**

Increase Fidelity of Responsive Items

Exclude Non-Responsive Items

Cognitive measures items (ADAS-Cc

Functional measures items (CDR)

Step-Wise Progression of Composites

CAMD
CRITICAL PATH INSTITUTE

1 - Individual Efforts

2008 – onwards

Composite & Cognition Scores developed by Industry & Academia

Pfizer, Eisai, AZ, Janssen, Lilly, Merck, Abbot Skinner et al , Hobart+Pfizer, etc.

2 - Start of cooperation

2009 – 2013

ADNI PPSB ADAS-Cog Plus Working Group

Funding: Merck, Roche, Pfizer Task to: J. Hobart and then D. Mungas

3 - Harmonization of Efforts

2012 – onwards

ADNI PPSB Data Mining Session & Clinical End Points Working Group

All ADNI PPSB members (27 companies)

1. Mapping past efforts & Data sources for validation
2. Instrument(s) for Mild-Prodromal AD & pre symptomatic AD
3. Cross analyses on selected candidates

4 - Regulatory Qualification

2013 – 2016

CAMD (C-Path Inst): pCOA Project

1. Submission Letter of Intent to FDA and EMA – Stage 1
2. Submission of Qualification request to FDA and EMA – Stage 2
3. Aim for approval of new Instrument

The Composite Score Alzheimer's Disease Composite Score (ADCOMS) Selected for the CAMD/pCOA Briefing Package

- Statistically-derived score designed to measure cognition and function longitudinally in amnestic MCI/Prodromal AD – linear progression model
- Consists of a weighted combination of ADAS-Cog, MMSE and CDR
  - Calculated using Partial Least Squares (PLS) regression analysis, fitted to a linear disease decline model; baseline as the relevant response variable

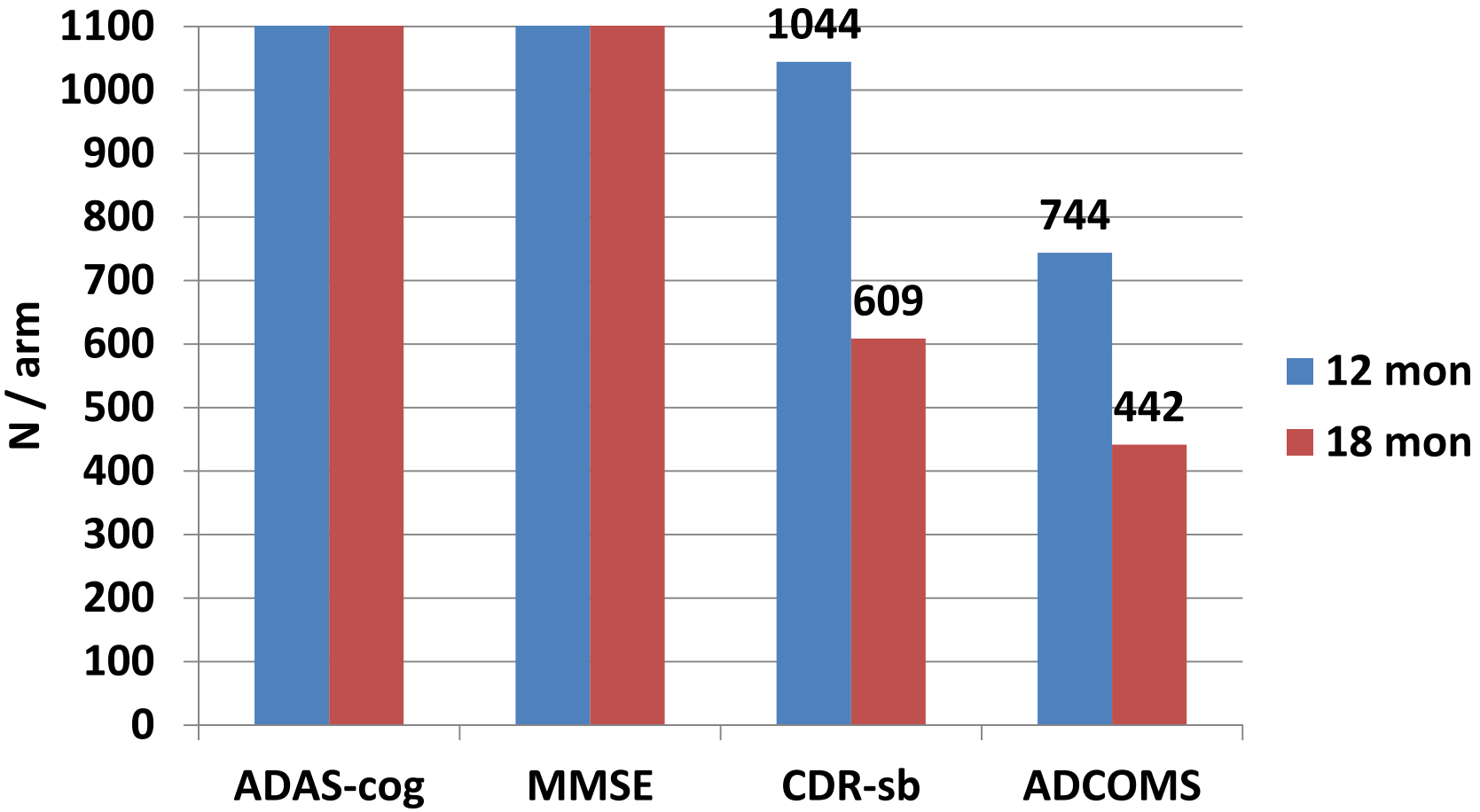
ADCOMS: Items and Their PLS Weight

Scale	Item ID	Item Name	PLS weight
ADAS-Cog	A4	Delayed Word Recall	0.0085
	A7	Orientation	0.0171
	A8	Word Recognition	0.0037
	A11	Word Finding	0.0162
MMSE	M1	Orientation Time	0.0416
	M7	Drawing	0.0382
CDR	C1	Personal Care	0.0543
	C2	Community Affairs	0.1091
	C3	Home and Hobbies	0.0890
	C4	Judgment and Problem Solving	0.0695
	C5	Memory	0.0587
	C6	Orientation	0.0782

ADCOMS:
Data Access

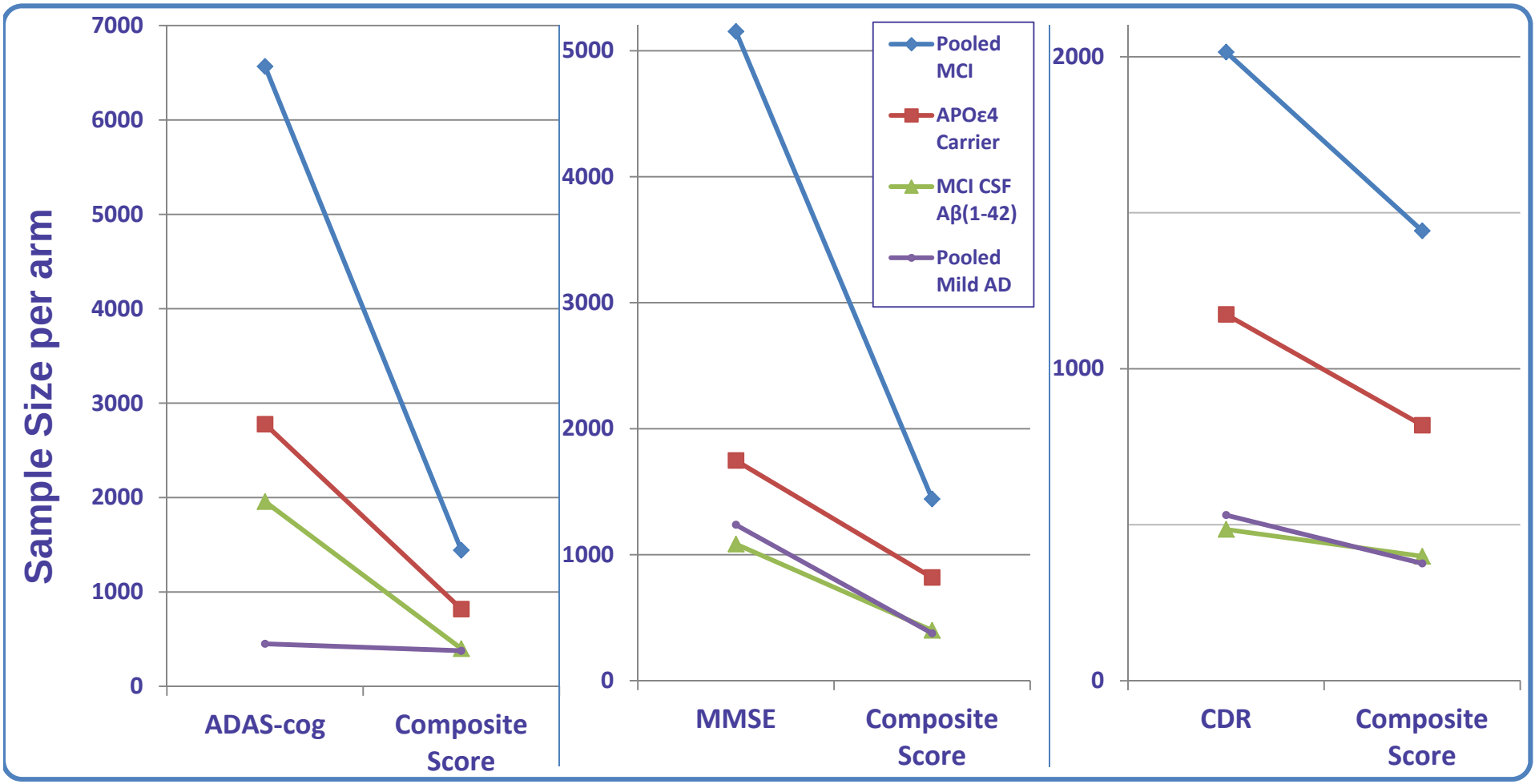
- Data for development – 12-mo placebo data from 4 studies:
  - **ADNI-1 MCI** (n=358; observational)
  - **ADCS MCI**: Donepezil and Vitamin E to delay conversion to AD (n=206; placebo)
  - **Donepezil Study 1**: 12 month donepezil vs placebo in MCI (n=312; placebo)
  - **Donepezil Study 2**: Donepezil 10 mg vs placebo on clinical and radiological markers in MCI (n=88; placebo)
- Prospective data will become available from ongoing Phase 2b study in Prodromal AD and Mild Alzheimer's Dementia
  - **BAN-2401** (NCT 01767311)**:** 12 & 18 months data
- Other possible sources of retrospective and prospective data from MCI/Prodromal AD studies are mapped and pursued
  - The pCOA Team looks for support form all CAMD members

ADCOMS Reduces the Needed Sample Size Required Compared to Original Scales

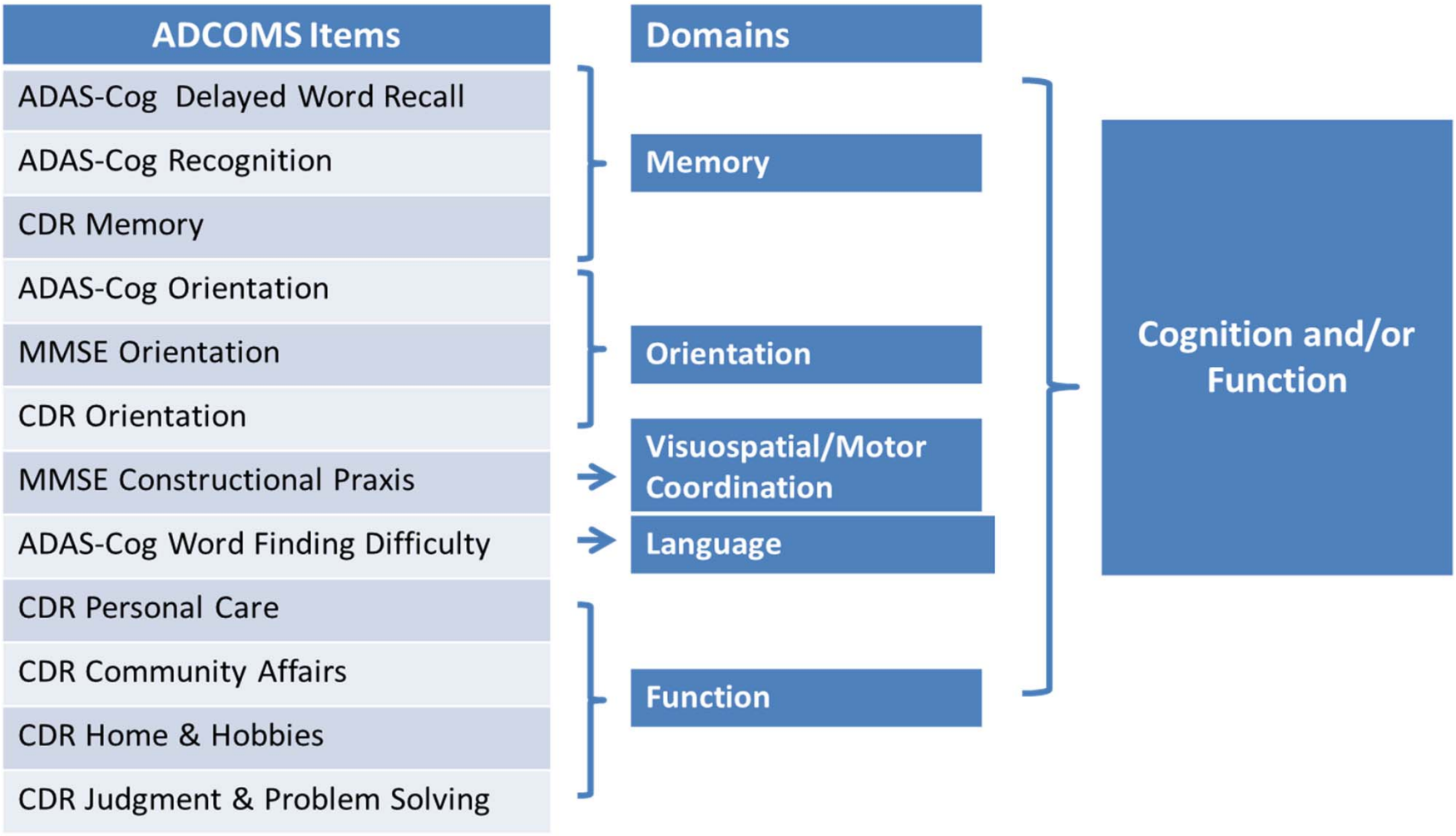


* CDR-sb required 40% more subjects compared to ADCOMS

Composite Score Improves Responsiveness / Sample Size Required Compared to Original Scales



ADCOMS measures clinically meaningful concepts



Why is Clinical Meaningfulness Important? Why Study It?

- Matters to patients and their family members
- Important to clinicians
- Essential to payers
  - Amyloid PET reimbursement
- Critically important to regulators
  - FDA recommended CAMD leverage qualitative research demonstrating that a proposed composite:

    "measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement of concept, population, and use."

Goals of this study:

- Identify the cognitive symptoms patients and informants endorse early in the disease
- Compare how this maps to the subcomponents of various composite endpoints

How do you Study Clinical Meaningfulness?

Quantitative measures

- Inclusion of CDR domains
- Conversion to AD Dementia
- Time/Progression along the AD Spectrum

Qualitative measures

- Patient Reported Outcome Measures
- Integrating voice of patient/informant
- Clinically meaningful domains mapped to ADCOMS

Methods – Frequency Grids

Leveraged qualitative research work completed for PRO

- Cognition Working Group of Critical Path Institute's PRO Consortium

  Qualitative Research Briefing Document Report

Frequency grids of reported concerns from focus groups

- Amnestic MCI (aMCI) participants
- Collateral Informants
- AD participants
- Healthy Controls

Categorized reported concerns into:

1. Concerns endorsed by a similar percentage

   <15% discordance between patient and informant reports

2. Concerns endorsed more frequently by aMCI participants

   >15% discordance w/more endorsement by patients

3. Concerns endorse more frequently by collateral informants

   >15% discordance w/more endorsement by informants

Methods: Narratives & Cognitive & Non-Cognitive Domains

Two independent expert Neuropsychologists

- Reviewed the narrative transcripts

Assigned primary & secondary domains

Primary: Most frequently described by patients and/or informants

Secondary: Ones described but endorsed less frequently

The raters identified and selected from the following cognitive and non-cognitive domains for each item of the PRO qualitative research study:

- Memory
- Executive Functioning
- Attention
- Language
- Visuospatial/Motor Coordination
- Orientation
- Neuropsychiatric
- Non-AD or Age-Related changes

Methods – Frequency of endorsement by Domain

Two independent expert raters calculated the frequency of endorsement by domain.

- Following independent reviews:
  - Met, reviewed and adjudicated findings
  - Alignment occurred >95% of the time
  - Not aligned ⇨ reviewed each transcript together & reached consensus

Entire exercise was completed twice by each rater

- Separated by approximately two months
- Results of original and follow-up were compared
  - Increase the replicability and validity of the findings

Methods – ADCOMS Analysis

Objective Memory Measures:

- ADAS-Cog Delayed Word Recall
- ADAS-Cog Word Recognition

Subjective Memory Rating:

- CDR Memory

Objective Orientation Measures:

- MMSE Orientation
- ADAS-Cog Orientation

Subjective Orientation Rating:

- CDR Orientation

Objective Visuospatial/Motor Coordination

- MMSE Constructional Praxis

Subjective Language Rating:

- CDR Word Finding Difficulty

Subjective Ratings of Function:

- CDR Personal Care; Community Affairs; & Home and Hobbies

Results & Conclusions

Limitations

- Spectrum of aMCI, course & anosognosia
- Reliability of informants: exposure, age & dynamics
- Bias associated with focus groups

Primary and secondary concerns of aMCI participants and collateral informants mapped onto:

- Memory
- Executive Functioning
- Language
- Orientation

Aligns with literature in healthy elderly through pAD

- Episodic Memory
- Timed Executive Functioning

Literature also supports that language/word finding and orientation difficulties are common problems in those people who:

- Progress into aMCI and Mild AD

Overall Conclusions

- Briefing document submitted in a field that is not settled. Discussions and exchanges of opinion amongst members helped shape the document.
- Consortium based effort provided cost and resource efficiencies.
- Data sharing critical for success of project

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pCOA Chairs: *Johan Luthman & Michael Ropacki*
Project management: *Hemaka Rajapakse*