Validation of a Precision Measure of Cognitive Change in a Phase II Clinical Trial in Early AD: The Early Mild Alzheimer's Cognitive Composite (EMACC)

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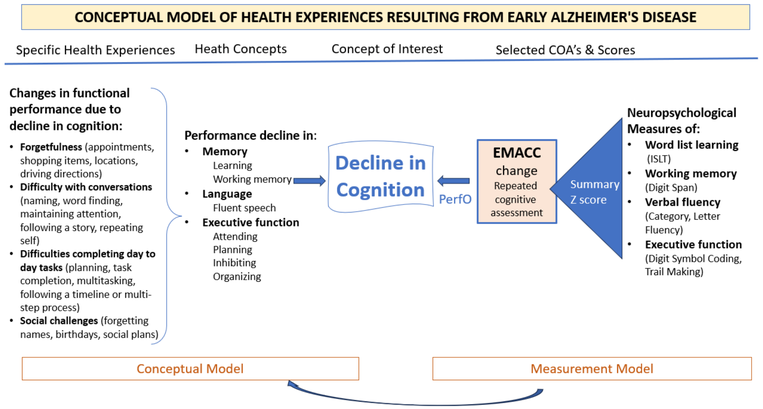
SUMMARY & CONCLUSIONS:

- Here we confirm that the **Early and Mild Alzheimer's Cognitive Composite** (**EMACC**, Jaeger et al., 2017) is a psychometrically superior cognitive endpoint for Early AD trials.
- Unlike ADAS-cog in Early AD, component scores are normally distributed with no floor or ceiling effects.
- The EMACC was empirically derived from four different longitudinal aging cohorts and is composed of well known clinical neuropsychological measures.
- **Development of EMACC is consistent with FDA Patient Focused Drug Development Guidance.**
- The EMACC has been used in large multi-national trials of early AD.
- We report here on the psychometric properties of the EMACC in an ongoing phase 2 clinical trial.
- Data confirm excellent distributional properties of the subtests, **test re-test reliability (screening to baseline) of r=0.94.**
- The **effect size difference on EMACC between CDR Global 0.5 and 1 was large (0.93).**
- **Adoption of the EMACC has the potential to streamline clinical trials, reducing patient burden and sponsor cost while advancing development of new therapies by using precise and clinically meaningful cognitive measures in early AD.**

Background

Cognitive measures with higher precision produce more robust and replicable signals with smaller sample sizes. The Early and Mild Alzheimer's Cognitive Composite (EMACC, Jaeger 2017) is an empirically derived composite of validated clinical neuropsychological tests statistically optimized for amyloid associated cognitive decline in early AD. Building on its development using multiple longitudinal aging cohorts, we report data from an ongoing phase II clinical trial that confirms feasibility and examines replicability and validation as compared to other endpoints.

EMACC Conceptual Model



Adapted from FDA COA Guidance

Methodology

- Data from ongoing phase II, double-blind, placebo-controlled trial of early Alzheimer's disease sponsored by INmune Bio were used in these analyses (ClinicalTrials.gov ID NCT05318976).
- Sites: Australia, Canada, Czech Republic, France, Poland, Spain, UK.
- Screening and baseline data for the EMACC, CDR, and MMSE (screening only), were included in the analyses.
- Mean duration between screening and baseline was 33.6 days (SD 11.5).
- Psychometric analyses: descriptive statistics to examine normality of distributions, Pearson correlations to evaluate test-retest reliability between screening and baseline visits and construct validity by way of associations with CDS-SB and MMSE. Paired-sample t-tests were used to evaluate practice effects between screening and baseline and ANOVA was used to estimate the difference on EMACC as a function of baseline CDR Global rating and diagnostic stratification (MCI vs. mild AD).

Participants

- Final baseline sample from Phase II trial.
- 207 participants diagnosed with MCI (Jack stage 3, n= 92) or Early dementia (Jack stage 4, n=115) of the Alzheimer's type.
- 51% Female, Mean age 73.14 years (SD = 6.41).

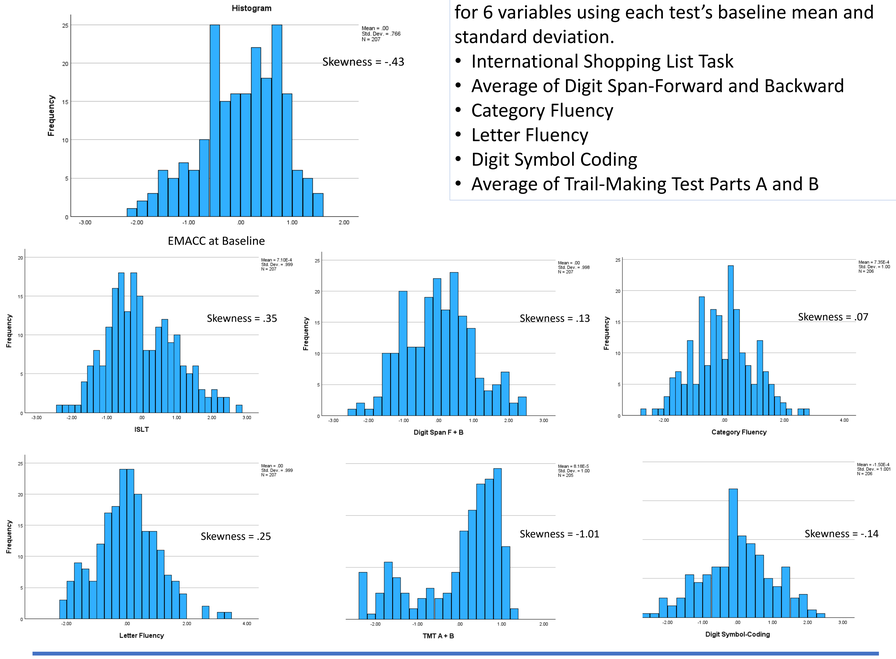
References:

Jaeger, J., Hagen, C., Loft, Henrik, Lim, Y., Aschenbrenner, A., Segerdahl, M., Tong, G., Mielke, M., Hassenstab, J., & Stricker, N. (2017, November) *Cognitive Endpoints for Early Alzheimer's Disease Trials: Development of the Early AD/ MCI Alzheimer's Cognitive Composite (EMACC). International Conference on Clinical Trials in Alzheimer's Disease (CTAD), Boston, MA, United States.*

U.S. Food and Drug Administration. *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*. June 2022.

Results

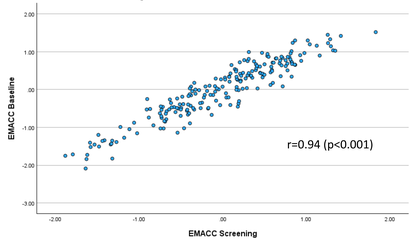
Baseline Distributions



The EMACC was computed by averaging the z-scores for 6 variables using each test's baseline mean and standard deviation.

- International Shopping List Task
- Average of Digit Span-Forward and Backward
- Category Fluency
- Letter Fluency
- Digit Symbol Coding
- Average of Trail-Making Test Parts A and B

Test-Retest Reliability

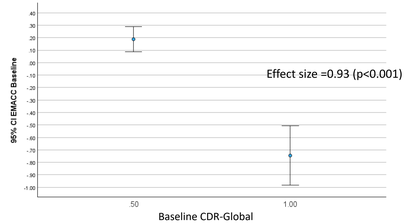


EMACC Component	Test-Retest Correlation
International Shopping List	r= .76**
Digit Span	r= .83**
Category Fluency	r= .81**
Letter Fluency	r= .76**
Trail Making Test	r= .87**
Digit Symbol Coding	r= .93**

** p<0.001 (2-tailed)

Note: Anticipated practice effects were noted on Digit Symbol Coding, but not EMACC score.

Criterion Validity: Association with CDR Global rating



Correlations between EMACC and CDR-SB (r=.62) and MMSE (at screening) (r=.57), were highly significant (both p<0.001).

Poster presented at ISCTM February 2025.