Item Response Theory Model as Support for Decision-Making: Simulation Example for Inclusion Criteria in Alzheimer's Trial

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OBJECTIVES

To demonstrate the use of Item Response Theory (IRT) in drug development (DD) decision-making.

To base the demonstration on a hypothetical investigation of inclusion criterion achieving highest probability to detect a drug effect in an Alzheimer's Disease trial.

METHODS

IRT model

■ IRT models, introduced in pharmacometrics[1,2,3], relate the response to each item of a test to a hidden variable (HV) denoted here ψ

■ An IRT model was suggested[1] to describe the cognitive subscale of the Alzheimer's disease assessment scale (ADAS-cog) and extended[4] to connect also the items of the mini-mental state examination (MMSE) to the cognition HV *(Figure 1)*

■ Baseline measurements from Alzheimer's disease neuroimaging initiative (ADNI)[5] data were used to inform the item-response component of the model and the placebo arm of a phase III study (LEADe)[6] supported the longitudinal model component: $\psi_i(t) = \psi_{0_i} + \alpha_i \cdot t$

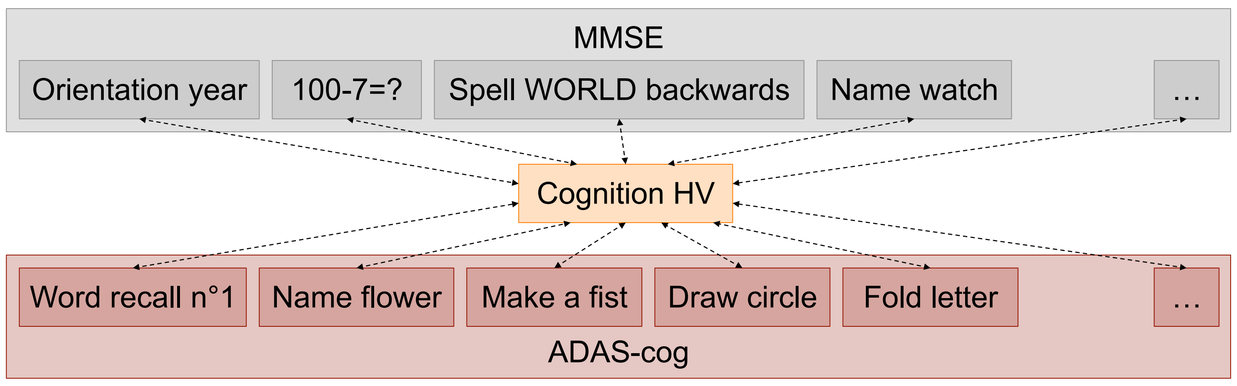

Figure 1: IRT model linking ADAS-cog and MMSE item scores to cognition hidden variable

DD question

■ Given a study design *(Figure 2)* with 600 patients, a planned repeated measures marginal means analysis, and an assumed disease modifying drug effect of 30% $\left(\overline{\alpha_i} = \alpha_i \cdot (1 - 0.3)\right)$

■ What is the MMSE inclusion range to consider?

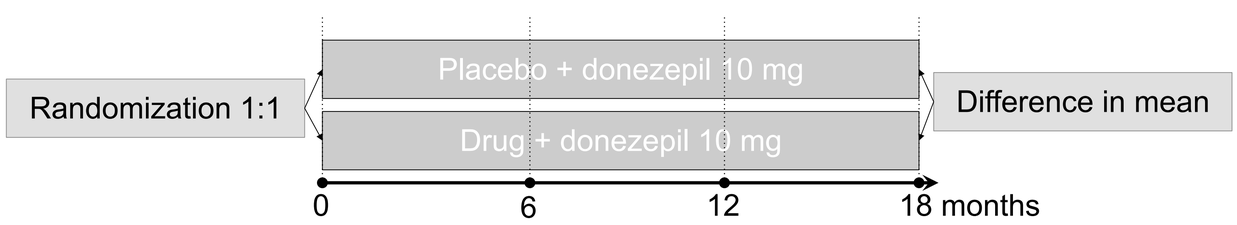

Figure 2: Design of a hypothetical Phase III study, based on the LEADe study

MMSE simulations

■ Sets of 500 simulations were generated and analyzed *(Figure 3)*

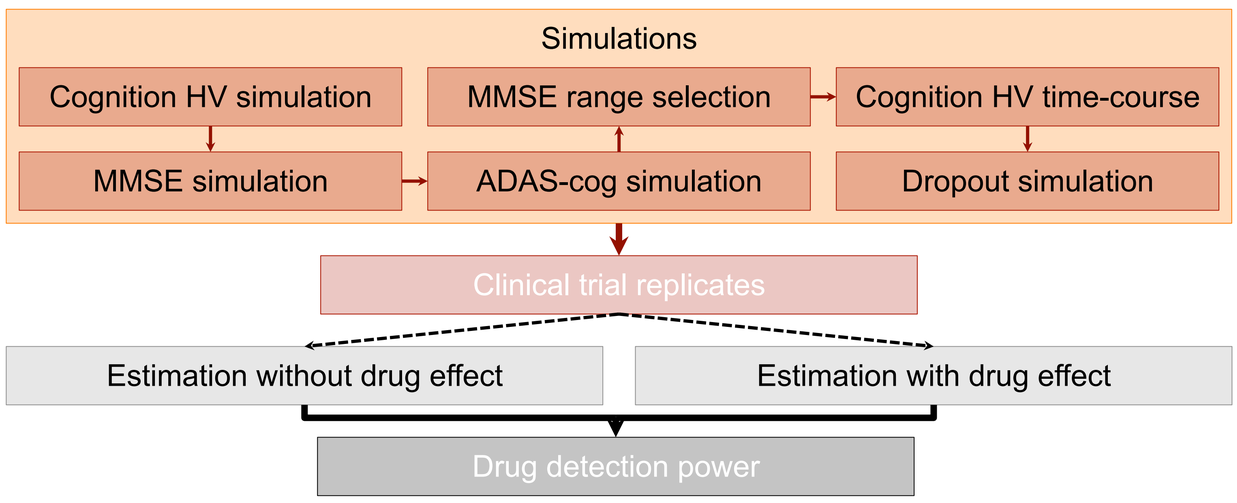

Figure 3: Algorithm used for stochastic simulations and estimations of clinical trial copies

CONCLUSIONS

The IRT pharmacometric approach allowed simulation of realistic clinical data and aided in supporting decision-making even though a statistical analysis was intended for the hypothetical trial.

This example highlights the utility of complex IRT models for drug development beyond data analysis.

RESULTS

MMSE simulations

■ MMSE inclusion ranges of 5 to 10, 10 to 15, 15 to 20, and 20 to 25 were investigated

■ The individual cognition hidden variables generated were used to simulate baseline MMSE and ADAS-cog scores *(Figure 4)*

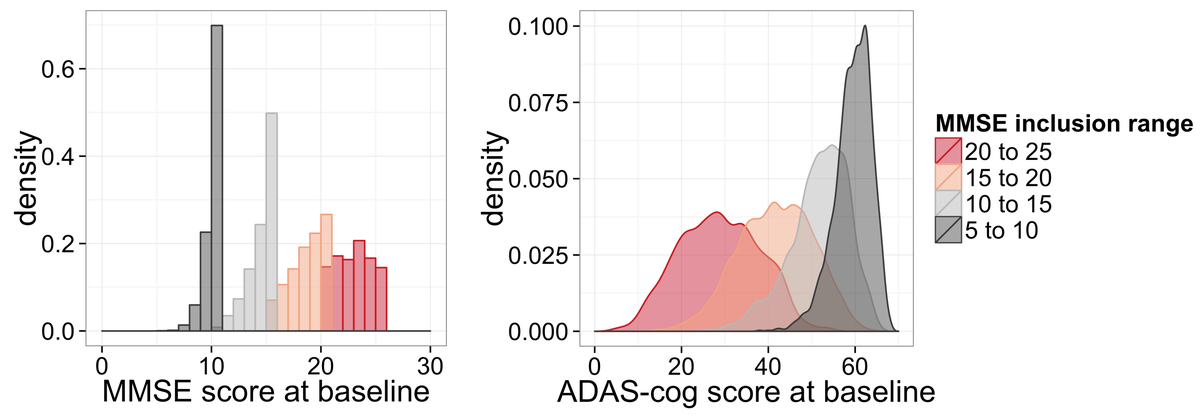

Figure 4: Distributions of MMSE and ADAS-cog scores obtained at baseline from the simulations of cognition HV corresponding to four MMSE inclusion ranges

ADAS-cog time-course

■ Individual longitudinal profiles over 18 months, unless dropout, were generated for both the placebo and the drug arms *(Figure 5)*

■ The repeated measures marginal means analysis was used for comparison of mean change from baseline (CFB) at last visit

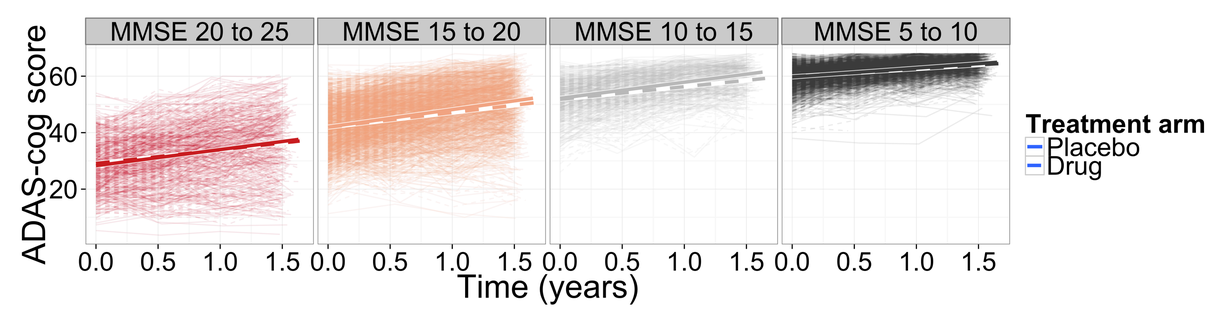

Figure 5: Individual time-course profiles in ADAS-cog score simulated from four MMSE inclusion ranges with a disease progression slope and a disease modifying drug effect

Power to detect drug effect

■ Log-likelihood ratio (LLR) tests were applied on the 500 clinical trial replicates to calculate the power achieved with each of the four MMSE inclusion ranges *(Figure 6)*

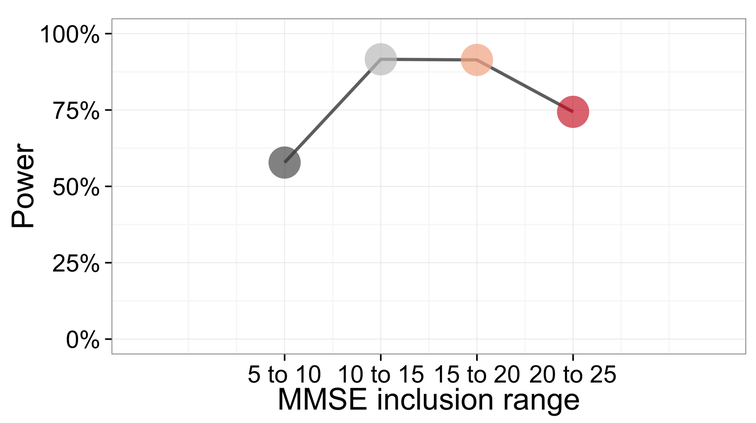

Figure 6: Power to detect simulated drug effect on cognition hidden variable through estimation of mean ADAS-cog CFB between two arms for four MMSE inclusion ranges

■ MMSE inclusion ranges of 10 to 15 and of 15 to 20 are predicted to have highest probability to detect disease modifying drug effect in hypothetical Alzheimer's disease clinical trial investigated

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