ADAS-Cog Placebo Response Modelling in Alzheimer’s Disease

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Background
Alzheimer Disease Assessment Scale (ADAS-Cog) is the standard clinical score used to assess cognition in Alzheimer’s Disease (AD). It is scored by number of errors ranging from 0 to 70 [1]. An increase in ADAS-Cog score implies worsening cognition. Several recent 6 month clinical trials of investigative medications for AD have failed to detect cognitive decline in placebo groups by ADAS-Cog, potentially obscuring true treatment effects. The lack of cognitive decline in the placebo groups has renewed interest in a better understanding of the time course of placebo response.

Objective
The aim of this work is to investigate the ADAS-Cog placebo response model in Alzheimer’s Disease to aid the design of future clinical trials by taking into account the information about which patients are more likely to be placebo responders.

Methods
Data from the placebo arms of 3 recent clinical trials (n=307) were pooled to investigate the placebo response as a function of time and disease severity given by Mini Mental Status Exam (MMSE). Mild AD severity was associated with MMSE > 18 and moderate AD severity was associated with MMSE ≤ 18.

Structural Identifiability Analysis
Identifiability Analysis was used to test whether the proposed model was structurally correct and appropriate for deriving clinically meaningful conclusions.

Model Validation
External model validation was carried out using data from internal GSK studies (n=733).

Results
The following figure shows the typical individual (blue line), population (red line) ADAS-Cog model predictions and observed data (circles). For each parameter, between-subject variability was tested and covariate analysis was investigated.

Conclusions
- Structural Identifiability is important for obtaining reliable predictions
- Model B adequately describes flat placebo response
- Including baseline MMSE score can improve predictions of ADAS-Cog response
  - Maximize the possibility of detecting clinical response

References