Population Dose-Response Model for ADAS-cog Scores in Patients with Alzheimer's Disease by Meta-Analysis of a Mixture of Summary and Individual Data

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Abstract

Motivation

• This modeling effort was originally evaluated as a project to explore different clinical designs for Alzheimer’s disease drug candidate selection.

• That required a longitudinal dose-response model for ADAS-cog suitable for examining individual and population data.

• Longitudinal dose-response models for ADAS-cog change from baseline were previously developed by multiple modelers using summary data (1), but these are not suitable for modeling individual inter-subject variability or for constructing population data summaries.

• Analysis of individual data from a small number of trials, though useful, would not respect the large body of evidence only available in the form of summary data.

• The element of issue: Simultaneous modeling of both summary and individual data.

• But can you rigorously combine such data in a model-based meta-analysis?

• Consider individual data in summary analysis and evaluate the issue:

• - Given problems: can’t combine individual data from modeling.

• - For summary data treatment arm are the super-patient and adjust only the residual variation for sample size.

• - Close but not completely adjusted the inter-patient variability components of the model.

• - Estimate the sampling distributions of summary statistics by simulation of missing individual data.

• - Very complex inference.

• - Don’t usually feasible as anything but for academic exercises.

• The focus here is to develop a new tool.

Methods

Data summary

Summary data

Table of mean ADAS-cog change from baseline for treatment arms in the three treatment groups:

- Placebo
- CP-457,920 60mg QD
- CP-457,920 120mg QD

Model for individual patient data

Model for sample means and variances

Results

The results are presented in terms of the adjusted marginal means with 95% Bayesian intervals per clinic.

Comparison of model predictions to observed data

The following plots show predicted mean ADAS-cog difference from placebo compared to observed values calculated from summary data. "Individual" predictions are posterior predictions for individual patients; "population" predictions are for hypothetical new observations in different patients and studies that share the same covariate values.

Conclusion

The proposed approach is a two-step procedure for developing a dose-responsive modeling for continuous endpoints for Alzheimer’s disease. The proposed modeling approach uses population data to develop a population model that can be used to predict responses in new patients. The individual patient data are then used to fit the population model and to assess the performance of the model.

References


Appendix: General derivation of modeling approach

Within this section, please provide a detailed derivation of the model equations and parameters used in the analysis. This should include any assumptions made, model structures, parameter definitions, and derivations of key expressions. The aim is to ensure that the mathematical underpinnings of the model are clear and accessible to readers.