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
William R. Gillespie1, James A. Rogers2, Koari Ito3, Marc R. Gastonguay1
1Metrum Research Group, Tariffville, CT; 2Pfizer Inc., New London, CT

Abstract

A. BACKGROUND/AIMS: Develop a population dose-response model for ADAS-cog based on both published summary statistics and individual patient data from a phase III trial.

B. METHODS: Summary statistics for ADAS-cog change from baseline were obtained from publications of results of 3 clinical trials in which placebo, donepezil, galantamine or rivastigmine were administered to patients with Alzheimer’s disease. Comparison of clinical trial and model predictions with summary data from the trials allows the model to be examined for predictivity. Predictive and posterior model-based meta-analyses were used to assess model performance. The model was evaluated for internal validity using predictive and posterior model-based meta-analyses. The model was developed to facilitate predictions of population means that may be used for simulations of individual patient outcomes. The model was subsequently applied to a recently completed trial and compared with observed data.

C. RESULTS: The proposed approach may be used to develop a population model that leverages both individual data and summary statistics. When the individual data model is linear with respect to inter-patient random effects, the sampling distributions for treatment means and variances are derived exactly. When the individual data model is not linear with respect to inter-patient random effects, the sampling distributions for treatment means and variances are approximated in 3 stages:

1. The sampling distributions are approximated as normal for the mean and gamma for the variance.
2. The conditional expectation for the treatment mean is approximated using the individual data model for which the variances of the inter-arm random effects are calculated and are used for sampling from the inter-arm variation.
3. The marginal expectation is approximated with the delta method.

D. CONCLUSION: The proposed approach may be used to develop a population model that leverages both individual data and summary statistics.

Motivation

This modeling effort was originally motivated by a project to explore different clinical trial designs for Alzheimer’s disease drug candidates via simulation.

A longitudinal dose-response model for ADAS-cog suitable for simulating individual patient data was developed. A model-based meta-analysis of summary data was developed. This was not suitable for simulating individual patient data.

Analysis of individual data from a small number of trials, though useful, would neglect the large body of evidence only available in the form of summary data.

The desired solution: Simultaneous modeling of both summary and individual data.

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

- Convert individual data to summary statistics and analyze as before:
  - Same problem: can’t simulate individual data from resulting model.
- For summary data treat each treatment arm like a super-patient and adjust only the residual variation for sample size.
- Does not correctly adjust the inter-arm variation components of the model.
- Estimate the sampling distribution of summary statistics by simulation of missing individual data.
  - Very compute-intensive.
  - Not usually feasible as anything but an academic exercise.
- This led us to develop a new method.

Background / Rationale

Data summary

Summary data

- Post-baseline sample means and sample variances for ADAS-cog change from baseline from published sources.
- Data set
  - Data from 55 studies / 81 treatment arms
  - 465 sample means
  - 253 sample variances

Individual patient data

- Results from two clinical trials
  - CP-457,201 dose-finding trial
    - 5 treatment arms / 196 patients: Placebo, 10 mg qd: 23 patients, donepezil 5 mg qd: 33 patients, CP-457,201 30 mg qd: 44 patients, CP-457,201 60 mg qd: 39 patients, CP-457,201 120 mg qd: 30 patients.
  - LEA1 trial
    - 3 treatment arms / 613 patients
      - Placebo + donepezil 10 mg qd / 20 months: 317 patients.
      - Abilify x donepezil 10 mg qd / 18 months followed by placebo + donepezil 10 mg qd / 2 months: 213 patients.
      - Abilify x donepezil 10 mg qd / 20 months: 77 patients.
- ADAS-cog change from baseline every 3 months for 18 months

Modeling approach

- The model was first conceptualized in terms of the individual data model.
- The sampling distributions for the treatment means and variances were then derived from that individual data model.
- Initial model structure was adapted from the Be et al model [1].
- Random effects structure included inter-trial and inter-unit variation (where unit = arm for summary data and unit = patient for individual data).
- Bayesian model fitting using WinBUGS 1.4.3
- Data management and analysis of MCMC samples using R
- Model evaluation primarily via graphical posterior predictive checking

Model for individual patients

ADAS-cog change from baseline on the jth occasion in the ith patient in the jth study:

\[
\Delta ADAS_{ijk} = \alpha_{ij} + \epsilon_{ij,k} \sim N(0, \sigma_{ij,k})
\]

Model for sample means and variances

Modifications for sample mean and variance of ADAS-cog change from baseline on the jth occasion in the ith treatment arm in the jth study:

\[
\Delta ADAS_{ijk} = \alpha_{ij} + \epsilon_{ij,k} \sim N(0, \sigma_{ij,k})
\]

Clinical trial and model predictions with individual data and summary data.

The results are based on 3 chains of 50,000 MCMC iterations each with 5,000 burn-in iterations per chain. The samples are thinned by 25 leaving a total of 5,400 MCMC samples for subsequent calculations and inferences.

Comparison of model predictions to observed data

The following plots show predicted treatment mean ADAS-cog difference from placebo compared to observed values calculated from summary data. Individual predictions are posterior predictions (posterior median and 95% credible intervals) for hypothetical new observations in the same patients and studies. Population predictions are posterior predictions for hypothetical new observations in different patients and studies that share the same covariate values.

Results

Conclusion

References

Appendix: General derivation of modeling approach
