The Value of Evidence Synthesis: Model-based Meta-analysis Based on the CAMD Database, the ADNI AD Cohort Data, and Literature Meta-data

James Rogers[1], Dan Polhamus[1], Kaori Ito[2], Klaus Romero[3], Ruolun Qiu[2], Bill Gillespie[1], Brian Corrigan[2]
(1) Metrum Research Group, Tarrifville, CT (2) Pfizer Inc, Groton, CT (3) Critical Path Institute, Tucson, AZ

BACKGROUND

A number of public data sources are available describing the progression of ADAS-cog scores in various sub-populations of mild to moderate Alzheimer's Disease (AD) under various trial conditions. These sources include the Coalition Against Major Diseases (CAMD) control arm database, data from the Alzheimer's Disease Neuroimaging Initiative's (ADNI) AD cohort, and literature meta-data.

OBJECTIVE

Our objective was to develop a model for clinical trial simulation that combined the unique insights afforded by each of the available data sources. As such, it was intended that the model provide characterization of placebo effects, drug effects (for already-marketed therapeutics), and rates of progression as a function of covariates. Moreover, it was intended that the model enable simulation of realistic patient-level data by correctly characterizing inter-patient variability and nonlinearities implied by the bounded nature of the ADAS-cog instrument.

METHODS

DATA
The development of the data sources contributing to our analysis has been described elsewhere. These sources are: the literature data set constructed and analyzed by Ito et al.[1], individual patient data from the AD cohort of the ADNI study (https://www.loni.ucla.edu/ADNI), and individual patient data from the CAMD control arm database (https://codr.c-path.org/main/login.html).

MODEL
A large number of features of previously published models were taken as starting points and were revisited only to the extent required to obtain satisfactory model diagnostics. These "accepted structural features" included:

- The use of a generalized logistic function to describe the natural progression of the disease on a constrained scale[2].
- The use of a Bateman-type function to describe the incremental placebo[3, 1].
- The use of Emax functions to describe the incremental effects of approved AChE inhibitors as a function of dose and time[1].
- The placement of candidate covariate effects in the model. Specifically, the use of baseline severity as a covariate on the model intercept, and the use of baseline severity, ApoE genotype, and baseline age as covariates on rate of progression [4, 2].
- The use of baseline age and baseline severity as covariates on the hazard of dropout [5].

In addition, a number of important innovations were also implemented:

- A Bayesian implementation is utilized, allowing for a probabilistically correct synthesis of literature meta-data with patient-level data. This allows for a particularly comprehensive analysis, leveraging all available data.
- The generalized logistic function for expected disease progression is used in conjunction with Beta-distributed residuals (i.e. "beta regression"), resulting in a predictive distribution that falls entirely within the allowable range of ADAS-cog scores (0–70) during simulation.
- The covariance structure is extended to include inter-study variation in intercepts and rates of progression (beyond the variation already reflected by measured study-level covariates).
- The covariance structure is extended to include inter-study heterogeneity in variance components. This allows the model to account for the likely scenario that studies differ in the quality of the methods and investigators (potentially resulting in residual distributions with different variances in different studies) and differ as well in the diversity of the enrolled patient populations (potentially resulting in different inter-subject variances in different studies).
- The joint distribution of covariates was modeled using a "general location model"[6]. This aspect of the model provided a mechanism for including records with missing covariate values.

METHODS

MODEL EVALUATION
Model evaluation was broadly comprised of convergence diagnostics, internal validation to assess goodness of fit, and external validation to assess predictive validity. Standard MCMC convergence diagnostics were used including sampling history plots, posterior density estimates, and Gelman-Rubin convergence diagnostics. Internal validation focused primarily on posterior predictive checks based on both study-specific predictions (conditional on study-specific random effect estimates) and marginal predictions (conditional only on covariate values).

EXTERNAL VALIDATION
In accordance with a pre-specified modeling plan, response data from one of the CAMD protocols was withheld from modeling scientists during the model development phase. The fitted model was then used to generate a predictive distribution for the withheld response data, given the covariate values for that study, in a manner identical to that used for the internal validation "unconditional" predictive checks. The predictive validity of the model was then assessed by graphically comparing the observed data to the model predictions.

RESULTS

KEY ELEMENTS OF EVIDENCE SYNTHESIS

- Literature meta-data provided the primary support for estimation of placebo and drug effect parameters.
- ADNI was used be used to support estimation of long-term underlying disease progression rates, between subject variability and covariate effects.
- CAMD data added unique value in its ability support estimation of inter- and intra- trial variance components and to validate the performance of a model in the context of actual long and short duration randomized trials.

MODEL EVALUATION
Convergence diagnostics (not shown) indicated adequate stability and identifiability of parameters estimates. Posterior predictive checks based on the training data set ("internal validation", also not shown) indicated that both means and variances were well characterized over time in both the natural history context (ADNI) and the randmized trial context.

EXTERNAL VALIDATION
The ability of the model to predict the response distribution for the test (response-withheld) data is shown in Figure 1. Following finalization of the model based on training data, covariate values for the test data set were used to generate a posterior predictive distribution for the 5th, 50th, and 95th population percentiles of ADAS-cog scores.

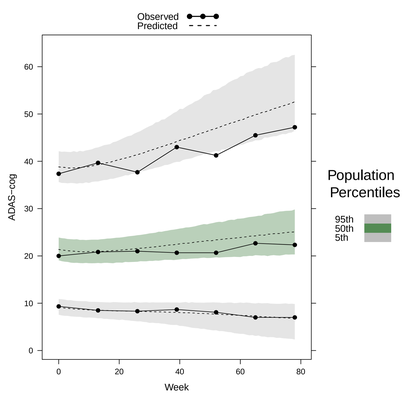

Figure 1: Visual predictive check for external validation. Dashed lines represent point estimate predictions, generated using the covariate values (but not the response data) for the test data set. Shaded regions represent 90% prediction intervals, incorporating parameter uncertainty.

RESULTS

MODEL SUMMARY
All covariate relationships of interest were included in the final model:

- Baseline ADAS-cog was modeled as dependent on baseline MMSE.
- Disease progression was modeled as dependent on time, baseline MMSE, ApoE genotype, baseline age, and gender.
- Study drop out was modeled as a function of time, baseline age, and baseline MMSE.

BMMSE	Gender	ApoE4	Median	5% LB	95% UB
16	Male	0	7.14	4.48	9.54
16	Male	1	7.07	4.49	9.42
16	Male	2	8.03	5.20	10.40
16	Female	0	6.53	3.73	9.05
16	Female	1	6.52	3.88	9.04
16	Female	2	7.55	4.76	9.78
21	Male	0	4.48	1.99	7.09
21	Male	1	4.43	2.06	6.94
21	Male	2	5.43	2.82	8.06
21	Female	0	3.97	1.42	6.57
21	Female	1	3.97	1.52	6.59
21	Female	2	4.88	2.16	7.17
26	Male	0	1.69	-0.28	4.12
26	Male	1	1.70	-0.33	4.00
26	Male	2	2.39	0.34	4.90
26	Female	0	1.36	-0.61	3.78
26	Female	1	1.35	-0.68	3.71
26	Female	2	2.01	0.02	4.53

Table 1: Posterior medians (point estimates) and 90% credible intervals for mean changes from baseline to one year in a naturally progressing population (i.e. placebo and drug effects not incorporated) as a function of baseline MMSE, gender, and ApoE genotype. (Age was also employed as a covariate on rate of progression, however due to collinearity amongst the covariates, age could not be varied independently for prediction purposes; in this table an age distribution was generated based on the other covariates.)

Age	Median	5% LB	95% UB
69	4.92	3.71	6.13
75	4.39	3.51	5.39
80	4.00	2.97	5.17

Table 2: Posterior medians (point estimates) and 90% credible intervals for mean changes from baseline to one year in a naturally progressing population (i.e. placebo and drug effects not incorporated) as a function of age. Reference values were used for other covariates: baseline MMSE = 21, ApoE4 negative, male.

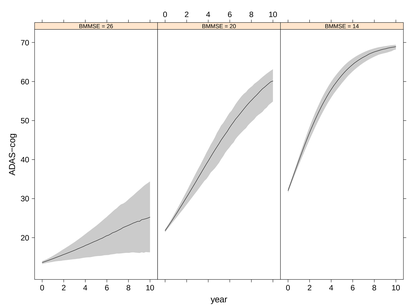

Figure 2: Lines represent posterior median predictions for a "typical individual" (i.e. with all random effects set to zero) and grey region represents the corresponding 90% credible interval for the predictions. Predictions past two years represent extrapolations beyond the extent of the available data, and are intended primarily to show that the mathematical implications of the model are consistent with the expected nonlinear progression of the endpoint.

RESULTS

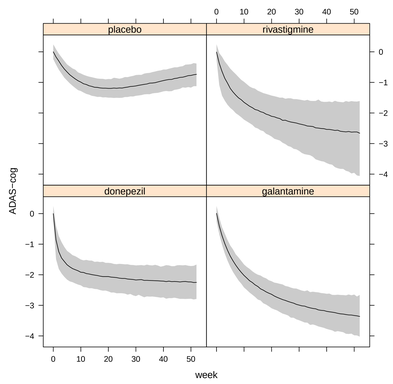

Figure 3: Model posterior median estimates and 90% credible intervals for the incremental effect of placebo (adjusted for natural progression) and for the incremental effects of donepezil 10 mg, galantamine 24 mg, and rivastigmine 6 mg (each adjusted for both natural progression and placebo).

CONCLUSIONS

The fitted meta-analytic model provides a comprehensive summary of all publicly available information related to drug effects, disease progression, and trial design. Clinical trial simulation based on this model enables realistic, objective, prospective assessments of the likely performance of a wide variety of clinical trial designs.

RESOURCES

The model as presented may be re-fitted using the following resources:

- R and WinBUGS code to fit the model is maintained as part of the Open Disease Models project: www.opendiseasemodels.org.
- The literature data set of Ito et al. [1] is also provided at www.opendiseasemodels.org.
- Access to the ADNI data is provided via the ADNI website, http://adni.loni.ucla.edu/.
- For details on CAMD: http://www.c-path.org/camd, and for access to the CAMD database: https://codr.c-path.org/main/login.html
- For information on an extended literature database and additional related models, see: www.metamodl.com.

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