Metrum Research Group is a global leader in biomedical modeling and simulation. Our expert services have supported efficient and informed decision making for more than 100 drug, biologic, device, and diagnostic development companies and over 250 R&D projects. For more information, please see metrumrg.com.

Alzheimer's Disease Overview

Uses of model-based methods to support strategic decision making in early phase trials:

- Assess probability of achieving target product profile given historical or partially observed data
- Futility analysis based on joint efficacy and dropout data at interim (Go/No Go) [1]
- Dose selection and optimization
- Assessment of expected trial design performances

The adsim trial simulation tool: This is the FDA reviewed and endorsed tool for simulation of clinical trials in the mild-to-moderate AD patient population, developed by MetrumRG and the C-Path Institute. This open source R package allows simple longitudinal simulation of patient profiles based upon a population dose-response longitudinal meta-analysis [2,3] of patients from ADNI, CAMD, and published literature results. Simulations using the tool may be used for:

- Sample size determination for complex designs
- Assessing optimal trial duration and effect measurement times
- Quantitative comparison of competing trial designs
- Determination of the most appropriate analytical methods for novel designs (e.g., tests for disease modifying effects)

METAMODL™

METAMODL™ is a library of disease-area content, including models, public source clinical data, and software tools, designed to support drug development decision-making via modeling and smiluation. Specific technologies employed are model-based meta analysis, multi scale systems pharmacology models, and nonlinear mixed effects disease progression models.

Current METAMODL™ disease areas include Alzheimer's Disease, Hepatitis C, Osteoperosis/Bone Health, Migraine prophylaxis, Multiple sclerosis, and non-small cell lung cancer.

New content in additional disease areas is currently under development and will be added throughout 2013. Access to the METAMODL™ library is available by subscription at various levels.

Metrum Research Group, LLC I 2 Tunxis Road, Tarifville, CT 06081 I (860) - 735 - 7043 I www.metrumrg.com I @Metrumrg

[1]James Rogers, Peter Lockwood, Dan Polhamus, Yves Brault, Anne Desmet, Kaori Ito, Klaus Romero, Ruolun Qiu, Bill Gillespie, Brian Corrigan, Marc Gastonguay, Model-based Analysis to Support Strategic Decision Making: A Case Study from the Development of a 5HT6 Antagonist for the Treatment of Alzheimer's Disease, *Alzheimer's Association International Conference, 2012* [2] Gillespie, William R. and Rogers, James A and Ito, Kaori and Gastonguay, Marc R, Population Dose-Response Model for ADAS-cog Scores in Patients with Alzheimers Disease by Meta-Analysis of a Mixture of Summary and Individual Data, *American Conference on Pharmacometrics, 2009.* [3] Rogers, James A and Polhamus, Daniel and Gillespie, William R and Ito, Kaori and Romero, Klaus and Qiu, Ruolun and Stephenson, Diane and Gastonguay, Marc R and Corrigan, Brian, Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis, *J Pharmacokinet Pharmacodyn, 2012, doi: 10.1007/s10928-012-9263-3.*

Clinical Dementia Rating Modeling and Simulation: *Joint progression of CDR and biomarkers in the ADNI cohort*

Daniel G. Polhamus, Ph.D., James A. Rogers, Ph.D., William R. Gillespie, Ph.D., Jonathan French, Sc.D.

Metrum Research Group, Tariffville, CT

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Background

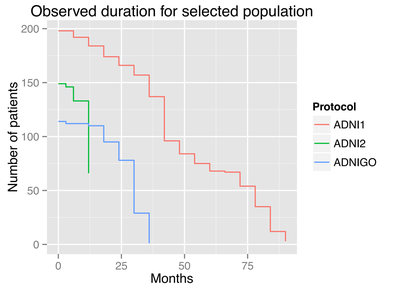
Future clinical trials in prodromal AD are expected to rely on CDR as an important efficacy endpoint as sensitivity of the CDR in the prodromal population is favorable compared to other common clinical endpoints [Cedarbaum et al., 2013]. Statistical models for the longitudinal progression of CDR scores provide a basis for more insightful analysis of clinical trial data, as well as a basis for better prospective understanding of the operating characteristics of candidate trial designs through simulating from the model. Models that describe CDR progression as a function of demographic covariates may be used to evaluate the likely impact of various trial enrichment strategies through simulation. Simultaneously modeling the longitudinal biomarker data allows us to examine the expected co-progression of clinical and pathological elements of the disease.

We propose modeling this joint progression via a latent variable approach as seen in item response theory (IRT) similar to the methodology seen in work in mild-to-moderate AD [Ueckert, 2012]. For CDR and the prodromal population, latent variable approaches exist for disease classification [Royall et al., 2012, Antila et al., 2013] but have not been extended to trial simulation. FDA reviewed and recommended tools and approaches for model based trial simulation in the mild-to-moderate population exist [Polhamus et al., 2013, Rogers et al., 2012], and our current effort seeks to enable similar but enhanced approaches for prodromal AD.

Methods: Data

Data was taken from the Alzheimer's Disease NeuroImaging (ADNI) database. We selected all patients diagnosed as MCI (early or late) at baseline who additionally had baseline CSF measurements (N=461).

Covariate	Mean	SD	5%	95%
Age	72.70	7.74	59.90	84.70
% ApoE4-+/+-	39.26			
% ApoE4++	10.63			
Baseline CDR sum	1.48	0.86	0.50	3.00
Baseline FAQ	3.07	4.05	0.00	12.00
Baseline MMSE	27.53	1.84	24.00	30.00
Baseline Tau/Abeta	0.57	0.52	0.11	1.47
% Female	38.39			
% Maternal dementia	42.08			
% Paternal dementia	20.82			
Yrs of education	15.98	2.83	12.00	20.00



Methods: Models

Efficacy model (co-progression):

A Bayesian hierarchical model was fit using OpenBUGS 3.2.2 (MCMC using the Gibbs sampler) and all priors were taken to be non-informative. Appropriateness of the model was assessed using visual predictive checks to ascertain that simulated data from the model replicates the observed data.

The co-progression model assumes patient i at time t_{ij} has some latent disease state, $\theta_i(t_{ij})$. At randomization, the distribution of latent status is standard normal for the "reference" patient (a male ApoE4 non-carrier with no familial dementia history, and covariates matching the baseline mean for the population). The disease state is then assumed to change linearly over time, with an intercept (corresponding to disease state at baseline, $t_{ij} = 0$) and slope unique to each patient, adjusted to the covariates listed in the demographics table (excluding baseline CDR sum of boxes). Observable responses (CDR item scores and volumetrics here) are modeled as functions of the latent disease state, e.g., endpoint l is modeled as:

$$Y_{ij}^{(l)} \sim f^{(l)}\left(y|\boldsymbol{\eta}^{(l)}, \theta_i(t_{ij})\right)$$

The function $f()$ is a probability distribution parameterized as a function of the latent status and a set of parameters ($\boldsymbol{\eta}^{(l)}$) specific to endpoint l.

Modeled endpoints:

Endpoint category	Item$^{(l)}$	$f^{(l)}$
CDR	Memory	Categorical
	Orientation	Categorical
	Judgement	Categorical
	Community	Categorical
	Home	Categorical
	Personal care	Categorical
Volumetrics	Ventricular	Lognormal
	Hippocampal	Lognormal
	Whole brain	Lognormal
	Entorhinal	Lognormal
	Fusiform	Lognormal
	Midtemporal	Lognormal
	Intracranial	Lognormal

Dropout model:

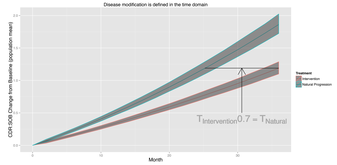
Clinical trial simulation requires both simulation of the efficacy endpoint and dropout. The ADNI database is not a good representation of the dropout pattern typically seen in clinical trials (it is heavily censored, there is no treatment incentive, etc...). Instead, we use the FDA published dropout model [Williams-Faltaos et al.] for the mild-to-moderate placebo treated population for demonstrative purposes. The model is a simple lognormal accelerated failure time-to-event model adjusting for age and baseline ADAScog11.

$$log(T) = \beta_0 + \beta_{age}\left(age - \overline{age}\right) + \beta_{adas}\left(adas - \overline{adas}\right) + \sigma\epsilon$$

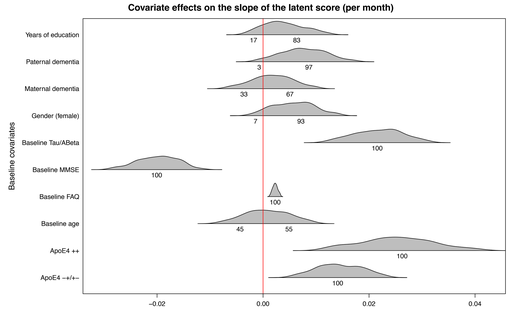
Methods: Simulations

Population simulations were evaluated using 5000 patients simulated with 1000 different parameter configurations from the joint posterior distribution. These quantify the expected population trend and parameter uncertainty.

Trial simulations, on the other hand, demonstrate trends expected from trial populations (smaller sample sizes, dropout, etc...). These were performed with the goal of detecting a 30% disease modifying effect (defined in the time domain). Power is defined as the ability to detect the difference using an MMRM analysis (two-sided with $\alpha = 0.05$).

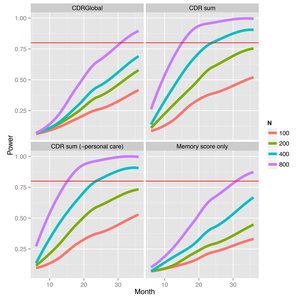


Results: Covariate effect on rate of progression



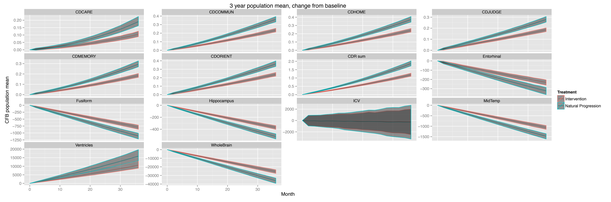
All covariates were normalized before inclusion in the model, and are thus directly comparable with regard to the magnitude of the effect. More positive values of the latent disease score indicate a higher level of disability.

Results: Trial simulation



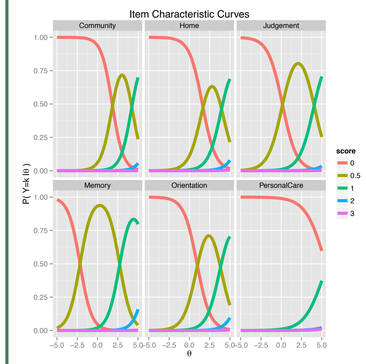
- Trials were simulated across a range of study sizes (N patients per study)
- CDR sum-of-boxes performs notably better than the memory component alone and global CDR
- No benefit is seen by omitting the personal care category

Results: Co-progression population simulations



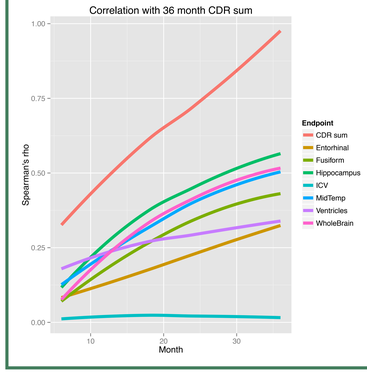
The population simulations show the expected population trend (no inter-individual variability). We compare the natural progression to a hypothetical treatment that reduces disease progression by 30%. Shaded regions are the 90% credible intervals for the population mean, shown as the solid line.

Results: CDR Item Characteristic Curves (ICC)



- The ICC's display the probability mass function of patient CDR score according to latent score
- The personal care score is 0 across nearly the entire range of latent scores for the ADNI prodromal patient population, indicating little information content for that item
- By definition, a patient with the reference covariate configuration has $\theta \sim N(0, 1)$ at baseline

Results: Evaluating early endpoints



- The correlation between the modeled volumetrics and the 36 month CDR sum of boxes was simulated over 1000 trials (the mean correlations are shown)
- Hippocampal volume is indicated as having the highest correlation of the modeled volumetrics to the likely primary (CDR sum)
- Highly correlated biomarkers are good candidates for inclusion in futility designs (i.e., informing early stopping rules)

Conclusions

This latent variable approach to modeling joint-progression of CDR and biomarkers in the prodromal AD population reinforces previous findings in the population, but more importantly provides an exploratory tool toward the design of future directions for trials. Notably:

- Our analysis of the baseline covariate demographics in this population show (in order of decreasing magnitude) ApoE status, MMSE and FAQ, Tau/ABeta ratio, paternal dementia, and gender as all having significant effects on the rate of progression. We can simulate future trials under enriched populations for various combinations of these effects.
- The model was used to demonstrate that the CDR sum of boxes performs significantly better than several alternative endpoints (CDR Global, and the memory component alone). Additionally, no gain in power was seen by removing the personal care item. Trial simulations can also be used for quantifying expected response and detecting abnormal study results.
- The model also allows us to evaluate the correlation between early endpoints and later sum-of-box scores for use in monitoring and futility analyses.

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