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 simulation. 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, Osteoporosis/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.

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

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Background
Past clinical trials in prodromal AD are expected to rely on CDR as an important efficacy endpoint as sensitivity of the CDR to the prodromal population is favorable compared to other common clinical endpoints (Cafarava 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 prespecified understanding of the operating characteristics of candidate trial designs through simulating from the model. Models that describe CDR progression as a function of demographics can be used to evaluate the likely impact of various clinical covariates through prospective 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 the 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 (Cook et al., 2012). For CDR and the prodromal population, latent variable approaches exist for disease classification (Boyal et al., 2012, Arora et al., 2013) but have not been extended to trial simulation. FDA reviewed and recommended tools and approaches for model based simulation in the mild-to-moderate population exist (Polkhaus et al., 2015, Rogers et al., 2015), and our current efforts seek 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).

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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 by using predictive checks to ascertain that simulated data from the model replicates the observed data.

The co-progression model assumes patient i at time t, x_i(t), has some latent disease state, s_i(t). At randomization, the distribution of latent state 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, s_i(0)) and slope unique to each patient, adjusted to the covariates listed in the demographics table (including baseline CDR sum of boxes). Observable responses (CDR item scores and volumetrics here) are modeled as functions of the latent disease states, e.g., endpoint is modeled as:

\[ y_i(t) = \beta_0 + \beta_1 s_i(t) + \epsilon_i(t) \]

The (function) f is a probability distribution parameterized as a function of the latent state and a set of parameters (\( \beta \)) specific to endpoint i.

The model was used to demonstrate that the CDR sum of boxes performs significantly better than the symptom component alone and global CDR.

Results: Evaluating early endpoints
The correlation between the modeled volumetrics and the 30 month CDR sum of boxes was simulated over 1000 trials (for the mean correlation is shown). Hippocampal volume is used as having the highest correlation of the modeled volumetrics in the likely primary (CDR sum) trials. Highly correlated biomarkers are good candidates for inclusion in Hardy disease (i.e., forming early stopping rules).

Methods: Simulations
Population simulations were outlined using 1000 patients simulated with 1000 different parameter configurations from the joint model. The model was fit using OpenBUGS 3.2.2 (MCMC using the Gibbs sampler), and all priors were taken to be non-informative. The simulations were performed with the goal of desirably 10% deviance deviance (defined in the same manner). Details are defined in the study paper (Polkhaus et al., 2015). Simulations were performed for the joint progression of CDR and biomarkers (joint model) and for trial simulating the model for the effect of the regimen under study on progression of CDR and biomarkers. 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 significant changes were observed for the regimen under study on progression of CDR and biomarkers. The model was used to demonstrate that the CDR sum of boxes performs significantly better than the symptom component alone and global CDR. The model was used to demonstrate that the CDR sum of boxes performs significantly better than the symptom component alone and global CDR.

Results: CDR Item Characteristic Curves (ICC)

The ICC displays the probability mass function of pairwise CDR score according to latest score.

The personal care score is 0 across nearly the entire range of latest scores for the ADNI prodromal patient population, indicating little information content for them.

By definition, a patient with the reference covariates configuration has \( s = 0 \) at baseline.

Results: Co-progression population simulations
The population simulations showed the expected population trend (the non-standardized variable). We complete the same progression in a longitudinal trial that induce disease progression by 30% (located relative to the 50% credible interval for the population mean, shown as the 0.0 line)