**From Evidence Synthesis to Trial Optimization: The adsim Package for Model-based Simulation in Alzheimer’s Disease**

Dan Polhaus, Jim Rogers, Bill Gillespie, Jonathan French, Marc Gastonguay

Metrum Research Group, Tariffville, CT

---

**Objectives**

Model-based drug development is ideally characterized by both comprehensive synthesis of available evidence as well as realistic simulation of future scenarios. To this end, a disease-drug trial model for Alzheimer’s Disease has been developed based on joint modeling of literature meta-data and individual patient data, summarizing available evidence with regard to rates of natural progression, placebo effects, and drug effects for marketed AD therapies [1, 2]. To facilitate broad use of the model in clinical trial simulation, a simulation package in R was developed. The adsim package provides functions and objects to simulate longitudinal ADAS-cog data, based upon the comprehensive model. Hyperthesized drug effects may be specified in a flexible manner, potentially including disease modifying components that are expressed relative to progression rates. Simulation of ADAS-cog trial results is then straightforward for a variety of designs that are typically of interest in stages of development ranging from phase 2a to phase 3.

**Methods**

**Data sources:**

- CAMD (http://www.c-path.org/)
- 14 studies, 26 placebo intervention patients
- ADNI (www.loni.ucla.edu/ADNI)
- ADNI: 1 study, 165 patients, varied disease progression
- Literature data set [3, 4]
- 18 studies reporting summary level endpoints
- Placebo, Donepezil, Galantamine, Rivastigmine

**Models:**

ADAS-cog:

For observations on patients in a study, Alzheimer’s disease modelled through a beta-logit model (1):

\[
\frac{\text{Pr} \left( \text{ADAS-cog} \leq k \right)}{1 + \text{exp} \left( \eta \right)} = \frac{\text{Pr} \left( \text{ADAS-cog} \leq k \right)}{1 + \text{exp} \left( \eta \right)}
\]

where:

- \( \eta \) = intercept (β0)
- Age (β1), Sex (β2), Apolipoprotein E status (β3), Disease duration (β4), Disease stage (β5), Global score (β6)

**Drop-out:**

A Weibull frailty model was used to describe drop-out as a function of history of age:

\[
f(t) = \text{Weibull}(\lambda, k) = \lambda \cdot k \cdot t^{k-1} \cdot \exp(-\lambda t^k)
\]

**adsim R package:**

Simple patient simulations, given treatments and regimens:

**Patient recruitment:**:

- Early Start
- Delayed Start
- Follow-up

**Methods: Candidate drug effect mechanism of action**

**Symptomatic:**

- Longitudinal effect profile similar to that of marketed AChE inhibitors, specified using an Emax functional form.
- Drug effect starts approximately a 2.5 point change in ADAS-cog at 24 weeks, onset ET50=1 week, half-life of effect=1 week.
- Candidate designs include 12 week parallel or 6 week cross-over trials.

**Disease Modifying:**

- Compounds that systematically reduce the rate of disease progression.
- Disease modifying effect is specified in the R package as a proportional type of virtual placebo progression. We drug effects with 20%, 30%, 40%, and 50% dose modifying compounds.
- Candidate designs include a 78 week parallel design and the delayed start design recently employed for Parkinson’s disease [5, 6].

**Methods: Parallel design**

**Methods: Cross-over design**

**Methods: Delayed start design**

**Results: Simulating a trial**

patients <- acRecruit( n=nPats, p=posteriorSample )
randomizedPatients <- acRandomize( patients, TrtSeqTab, TrtParTab )
simulatedProfiles <- acRun( p=posteriorSample, randomizedPatients, assessmentTimes, drop=TRUE )

**Methods: Delayed start design**

**Results: Simulations**

**Symptomatic:**

- Disease modifying Placebo Symptomatic

**Disease modifying:**

- Placebo Symptomatic Symptomatic:Placebo

**Conclusion**

The adsim package provides the knowledge and results from the most comprehensive AD model to date in a convenient, easy to use format. Using this package, simulation of comparative trials reflecting both hypothetical beliefs and historical data allows the researcher to informatively choose trial formats that more adequately answer their questions.

The package architecture was sufficiently robust to accommodate the outlined trials and the simulation-based estimates of assurance in the parallel group designs are in agreement with the theoretical power estimates. As expected, the 6 week cross-over design is shown to be favorable to the 12 week parallel group design. Also, the simulations indicate the parallel design as favorable in detection of disease modifying effects.

Supporting code and documentation for the current implementation of the model, based on the publicly available data sources, is available from www.openadisim.org. Further model development, including modeling of ADAS-cog sub-scores and key biomarkers, is ongoing as part of the METAMODS project. For more details see www.metamodi.com

---

**References**


[2] Bhattaram, V., Siddiqui, O., Kapcala, L. and Gobburu, J. Endpoints from phase 2a to phase 3. Based upon the comprehensive model. Hypothetical trials to simulate longitudinal ADAS-cog data, based upon the comprehensive model. Hyperthesized drug effects may be specified in a flexible manner, potentially including disease modifying components that are expressed relative to progression rates. Simulation of ADAS-cog trial results is then straightforward for a variety of designs that are typically of interest in stages of development ranging from phase 2a to phase 3.

[3] Park, K., Corrigan, B., Souza, D. and Eshoo, L. The value of evidence synthesis: Model-based estimates of assurance in the parallel group designs are in agreement with the theoretical power estimates. As expected, the 6 week cross-over design is shown to be favorable to the 12 week parallel group design. Also, the simulations indicate the parallel design as favorable in detection of disease modifying effects.

