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

Dan Polhamus, 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 therapeutics [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. Hypothesized 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/`)
  - 8 studies, 2518 placebo intervention patients
- ADNI (`www.loni.ucla.edu/ADNI`)
  - 1 study, 185 patients, natural disease progression
- Literature data set [3, 4]
  - 58 studies reporting summary level endpoints
  - Placebo, Donepezil, Galantamine, Rivastigmine

Models:

ADAS-cog:
For observation i on patient p in study k, ADAScog was modeled through a beta-logit model [1]:

$$\mathrm{E}\left[ADAS_{ipk}/70 \,|\, \text{patient } p\right] = \theta_{ipk},$$

$$g(\theta_{ipk}) = \eta_{pk} + \alpha_{pk} t_{ipk} + E_{\mathrm{PBO}}(t_{ipk}) + E_{\mathrm{DRG}}(t_{ipk}, D_{ipk}).$$

- Covariates are included on:
  - Intercept (η): bMMSE
  - Slope (α): bMMSE, Age, ApoE4, Gender
- Drugs: Donepezil, Rivastigmine, Galantamine

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

$$T_{pk} \sim \text{Weibull}(\alpha, h_{pk})$$

$$log(h_{pk}) = \beta_{\text{STUDY},k} + \beta_1 (bMMSE_{pk} - 21) + \beta_2 (bAge_{pk} - 75).$$

adsim R package:

Simple patient simulation, given treatments and regimens:

Patient recruitment:

- *acRecruit()*: Generates patients, their demographics, and a parameter vector of the model posterior characterizing disease state. Demographics are simulated from a provided covariate model or, if desired, an alternative provided by the user

Patient randomization:

- *acRandomize()*: Use a randomization function (block randomization by default) to assign patients to treatment arms. Arms are parameterized by specifying treatment time intervals (by arm) and treatments are parameterized by specifying symptomatic (E_{max}, ET_{50}) and dose modifying (DM) effects (proportional decrease in slope).

ADAS-cog simulation:

- *acRun()*: Given the randomized and parameterized patients, simulate ADAScog scores with or without interstudy variability. Specify $drop = TRUE$ to simulate patient drop-out.

References

[1] Gillespie, W.R., Rogers, J.A., Ito, K. and Gastonguay, M.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. In *American Conference on Pharmacometrics* (Mashantucket, CT, 2009).

[2] Rogers, J.A., Polhamus, D.G., Ito, K., Romero, R., Qiu, R., Gillespie, W.R. and Corrigan, B. The value of evidence synthesis: Model-based meta-analysis based on the CAMD database, the ADNI AD cohort data, and literature meta-data. In *ASCPT Annual Meeting* (Washington D.C., 2012).

[3] Ito, K., Corrigan, B., Zhao, Q., French, J., Miller, R., Soares, H., Katz, E., Nicholas, T., Billing, B., Anziano, R., Fullerton, T. and Alzheimer's Disease Neuroimaging Initiative. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. *Alzheimers Dement* **7** (2011):151–60.

[4] Ito, K., Rosario, M., Ahadieh, S., Corrigan, B.W., French, J., Fullerton, T., Zhang, R., Lockwood, P., Zhao, Q., Qiu, R., Russell, T. and Tensfeldt, T. A Disease Progression Meta-analysis Model for Cognitive Deterioration with Alzheimer's Disease. *Clin Pharmacol Ther* **83** (2008):S40.

[5] D'Agostino, Sr, R.B. The delayed-start study design. *N Engl J Med* **361** (2009):1304–6.

[6] Bhattaram, V., Siddiqui, O., Kapcala, L. and Gobburu, J. Endpoints and Analyses to Discern Disease-Modifying Drug Effects in Early Parkinson's Disease. *AAPS J* (2009).

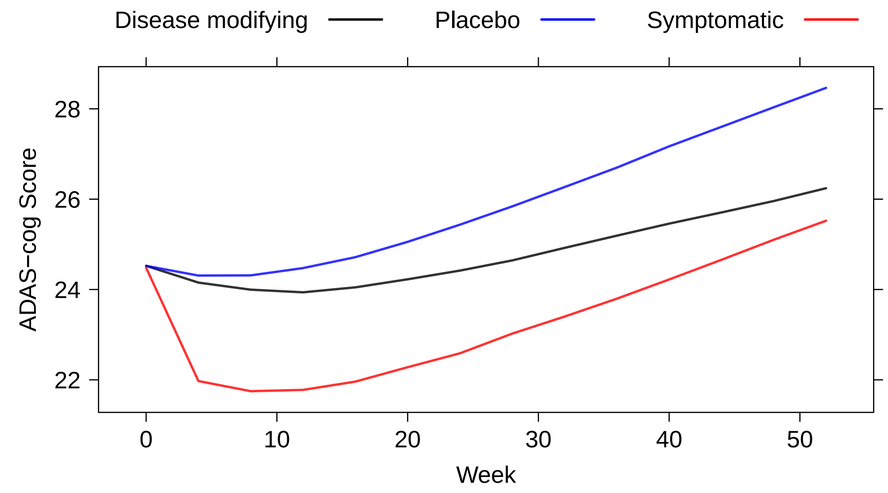
Methods: Candidate drug effect mechanism of action

Symptomatic:

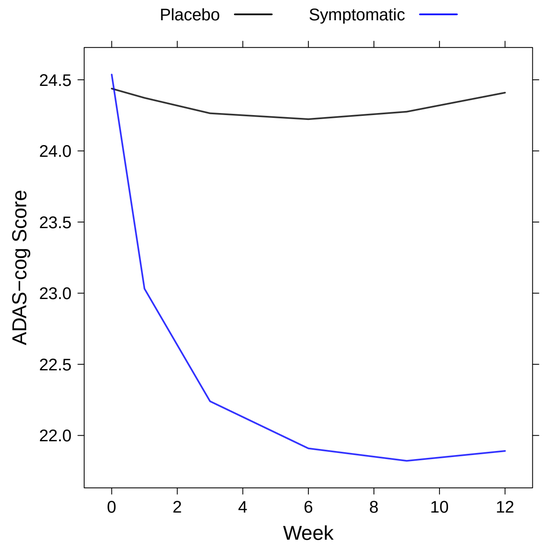
- Longitudinal effect profile similar to that of marketed AChE inhibitors, specified using an Emax functional form.
- Donepezil shows approximately a 2.5 point change in ADAS-cog at 24 weeks, onset ET50=1 week, half-life of offset=1 week.
- Candidate designs include 12 week parallel or 6 week cross-over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

Disease Modifying:

- Compounds that systematically reduce the rate of disease progression.
- Disease modifying effect is specified in the R package as a proportional inhibition of typical value 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].



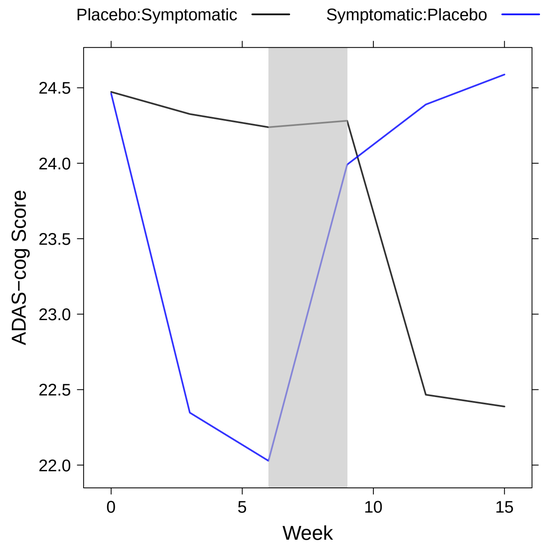
Methods: Parallel design



TrtParTable	DrugDose	emaxSx	et50Sx	et50SxWash	eDm
	Placebo	0.0	1	1	0
	Symptomatic	−2.5	1	1	0

TrtSeqTable	Arm	DrugDose	DoseBegin	DoseEnd
	A	Placebo	0	12
	B	Symptomatic	0	12

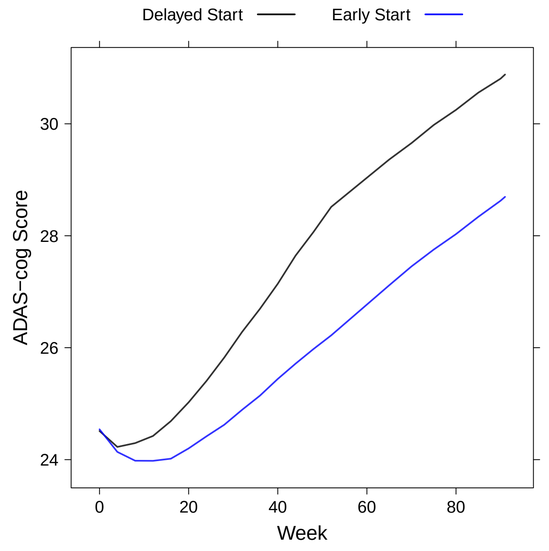
Methods: Cross-over design



TrtParTable	DrugDose	emaxSx	et50Sx	et50SxWash	eDm
	Symptomatic:Placebo	−2.5	1	1	0
	Placebo:Symptomatic	−2.5	1	1	0

TrtSeqTable	Arm	DrugDose	DoseBegin	DoseEnd
	A	Symptomatic:Placebo	0	6
	B	Placebo:Symptomatic	9	15

Methods: Delayed start design



TrtParTable	DrugDose	emaxSx	et50Sx	et50SxWash	eDm
	Early Start	0	1	1	0.5
	Delayed Start	0	1	1	0.5

TrtSeqTable	Arm	DrugDose	DoseBegin	DoseEnd
	A	Early Start	0	91
	B	Delayed Start	52	91

Results: Simulating a trial

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

Results: Simulations

Symptomatic:

Design	Relative Bias (%)	Power
6 week cross-over, n=30/arm	-14.20	0.87
12 week parallel, n=75/arm	-7.82	0.78

Disease modifying:

Effect	Design	P(reject H_0^1)	P(reject H_0^1 & H_0^2)	H_0^3 5% LB*	H_0^3 95% UB*
20 %	78 week parallel, n=600/arm	0.54			
20 %	91 week delayed start, n=600/arm	0.43	0.27	-0.757	0.733
30 %	78 week parallel, n=600/arm	0.76			
30 %	91 week delayed start, n=600/arm	0.66	0.46	-0.772	0.712
40 %	78 week parallel, n=600/arm	0.86			
40 %	91 week delayed start, n=600/arm	0.82	0.62	-0.783	0.696
50 %	78 week parallel, n=600/arm	0.93			
50 %	91 week delayed start, n=600/arm	0.90	0.74	-0.781	0.694

* Typical (median) lower and upper bounds for the (treatment-placebo) difference in mean change during the last 6 months of the trial.

H_0^1 : No difference in mean ADAS-cog change from baseline at week 52

H_0^2 : No difference in mean ADAS-cog change from baseline at week 91

H_0^3 : Difference in mean ADAS-cog change from week 65 to 91 exceeds a given threshold

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 accomodate 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.opendiseasemodels.org`. Further model development, including modeling of ADAS-cog subscores and key biomarkers, is ongoing as part of the METAMODL project. For more details see

`www.metamodl.com`