Towards FDA and EMA Endorsement* of a Clinical Trial Simulation Tool for Amnestic Mild Cognitive Impairment

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Background and Objectives

- There is an increased focus on evaluating Alzheimer disease (AD) drug candidates at earlier disease stages.
- Challenges in early AD clinical trials include: (a) slow rate of change in clinical outcomes over the study duration, and (b) patient pathophysiological uncertainty and heterogeneity.
- Therefore, an improved understanding of rates of change and its predictors for registration endpoints is critical for optimal trial design.
- This effort aims to develop a disease progression model-based clinical trial simulation tool to help inform clinical trial design in subjects with amnestic mild cognitive impairment (aMCI). The analysis endpoint was the Clinical Dementia Rating scale – Sum of Boxes (CDR-SB).

Methods

- Subject-level data from three sources – the ADNI (Alzheimer's Disease Neuroimaging Initiative) ADNI-1 and ADNI-2 observational studies, and the Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon (InDDEx) trial placebo arm – yielded a total of 1,051 aMCI subjects with 7,860 CDR-SB timepoints in the screening-to-48 months interval.
- The disease progression model was built using ADNI data (n=702), with InDDEx being reserved for external validation.
- The time course of CDR-SB was described by a non-linear mixed-effects model.
- Based on prior knowledge and/or clinical interest, the pre-specified covariates were: baseline intracranial volume-adjusted hippocampal volume (ICV-HV), sex, baseline mini-mental-state-examination (MMSE), baseline age, and apolipoprotein-E (*APOE*) genotype.

Results

- The generalized logistics model by Richards best captured the non-linear time course of CDR-SB scores. The **Table** presents the parameter estimates, with its respective predictors.
- The **Figure** demonstrates an application of the model. Clinical trial simulations were performed to inform sample size for various enrichment scenarios.

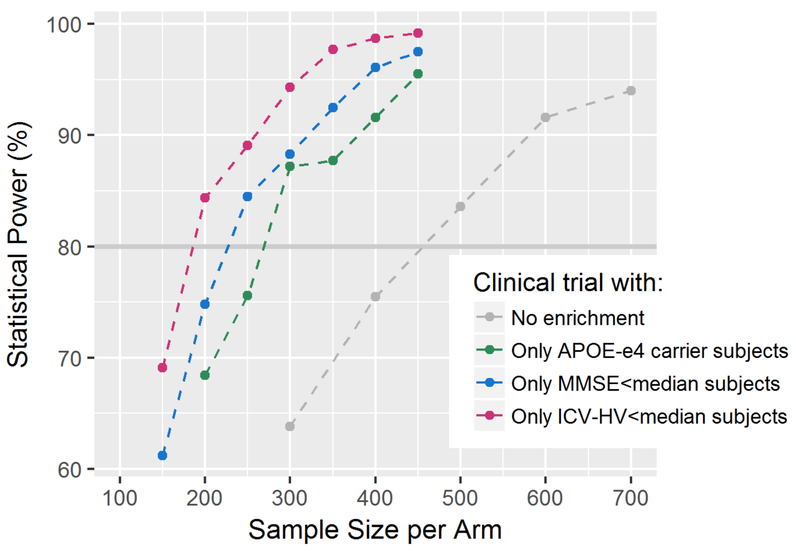

Figure **Statistical power *vs.* sample size for simulated placebo-controlled parallel group enriched and non-enriched clinical trials**

Enrichment scenarios are for FreeSurfer™ ICV-HV, APOE and MMSE. Thresholds for enrichment are illustrative. The simulations used: (a) the frequentist FreeSurfer™ covariate model; (b) a hypothetic drug effect of 50% reduction in the disease progression rate; (c) the developed dropout model. Number of simulations was 1,000 for each non-enriched or enriched scenario. Acronyms: APOE = Apolipoprotein E gene, ICV-HV = intracranial volume-adjusted hippocampal volume, MMSE = mini-mental state examination.

**For FDA, the Fit-for-Purpose Initiative; for EMA, the Qualification of Novel Methodologies for Drug Development.*

Table **Interpretation of parameter values, covariates effects, and their relationships[1,2]**

Parameter	Frequentist FOCE Population estimate	Transformation or parameter-covariate relationship	Interpretation for the population estimate at the original scale	Bayesian NUTS Median estimate (2.5th, 97.5th)
Baseline (points)	0.081	$\text{Baseline}' \times 18$ Where Baseline' denotes the estimated typical baseline CDR-SB within the (0, 1) interval; the 18 points denotes the highest possible observed CDR-SB score.	The estimated baseline CDR-SB score is 1.5 points	0.081 (0.078, 0.085)
MMSE effect on baseline (centered at 27.5 points)	-2.2	$\text{Baseline} \times \left(\frac{\text{MMSE}}{27.5}\right)^{-2.2}$	A decrease in baseline MMSE score from 27.5 to 26.5 is associated to approximately 8% increase in baseline CDR-SB score	-2.2 (-2.8, -1.6)
Intrinsic progression rate (year^{-1})	0.13	$\frac{\text{dScore}_i}{\text{dt}} = r_i \times \text{Score}_i \times \left[1 - \left(\frac{\text{Score}_i}{\max(\text{Score}_i)}\right)^{\beta}\right] \times 18$ $0.13 \times 0.081 \times (1 - 0.081^{3.3}) \times 18$	The estimated typical rate of change in CDR-SB score is 0.2 point/year	0.12 (0.088, 0.15)
Age effect on rate (centered at 73 years old)	1.5	$\text{Rate of change} \times \left(\frac{\text{Age}}{73}\right)^{1.5}$	An increase in age from 73 to 74 years old is associated to approximately 2% increase in CDR-SB progression rate	1.5 (0.046, 3)
Female sex effect on rate	1.3	$\text{Rate of change} \times 1.3$	Females have approximately 30% higher CDR-SB progression rate than males	1.3 (1, 1.7)
MMSE effect on rate (centered at 27.5 points)	-3.2	$\text{Rate of change} \times \left(\frac{\text{MMSE}}{27.5}\right)^{-3.2}$	A decrease in baseline MMSE score from 27.5 to 26.5 is associated to approximately 12% increase in CDR-SB progression rate	-3.1 (-5.1, -1.2)
APOE-ε4 non-carrier effect on rate	0.60	$\text{Rate of change} \times 0.6$	*APOE*-ε4 non-carriers have approximately 40% lower CDR-SB progression rate than carriers	0.60 (0.41, 0.79)
ICV-HV effect on rate[3] (centered at 5.29 cm^3)	-0.81	$\text{Rate of change} \times [1 - 0.81 \times (\text{ICVHV} - 5.29)]$ $\text{Rate of change} \times [1 - 0.52 \times (\text{ICVHV} - 7.54)]$	A 1-cm^3 decrease in baseline ICV-HV is associated to approximately 81% increase in CDR-SB progression rate	-0.84 (-1.2, -0.49)
Missing ICV-HV effect on rate	1.7	$\text{Rate of change} \times 1.7$	On average, the group of subjects with missing ICV-HV have approximately 70% higher CDR-SB progression rate than the subjects with a ICV-HV of 5.29 cm^3	1.7 (1.1, 2.4)
Shape factor of the Richards' model	3.3	$\text{Inflection point} = \left(\frac{1}{1 + \text{shape}}\right)^{1/\text{shape}} \times 18$	The inflection point of the rate of change in CDR-SB is estimated to occur at a score of approximately 11.6 points	4.6 (-0.17, 9.5)
Variance of baseline random effects	0.25	$\text{Coefficient of variation} = \sqrt{e^{0.25} - 1} \times 100$ Where log-normally distributed between-subject variability was estimated for the baseline scores to prevent the prediction of nonsensical scores at the subject level.	The coefficient of variation for the baseline CDR-SB scores is approximately 53%	0.25 (0.21, 0.29)
Covariance between baseline and rate random effects	0.046	$\text{Correlation coefficient} = \frac{0.046}{\sqrt{\text{variance of baseline}} \times \sqrt{\text{variance of rate}}}$	The correlation coefficient between baseline and rate random effects is 0.37	0.046 (0.033, 0.06)
Variance of rate random effects	0.062	$\text{Coefficient of variation} = \frac{\sqrt{0.062}}{\text{intrinsic progression rate}} \times 100$	The coefficient of variation for the CDR-SB intrinsic progression rate is approximately 196%	0.063 (0.052, 0.075)
Dispersion factor of the beta distribution	57	$\text{Standard deviation} = \frac{\text{Score}' \times (1 - \text{Score}')}{57 + 1}$ Where Score' denotes the expected CDR-SB score of the beta distribution within the (0, 1) interval.	At the typical baseline CDR-SB score, the standard deviation of the beta distributed residual variability is 0.036 points	57 (54, 60)
Condition number	15	Not applicable	Condition number is the ratio of the largest to the smallest eigenvalue of the covariance matrix, and measures ill-conditioning. There is no consensus in the literature of what constitutes a large condition number. In the field of Pharmacometrics, it is commonly accepted that a condition number exceeding 1,000 is indicative of severe ill-conditioning.	17

[1] CDR-SB scores were constrained to an open unit interval (0, 1) for implementation of the beta regression.
[2] Unless otherwise specified, estimates are for typical (or "average") subjects: male, 73-year old, *APOE*-ε4 carrier, 27.5-point MMSE, and 5.29 cm^3 LEAP™ ICV-HV. The effect of a covariate change on a parameter estimate assumes that the other covariates are held constant and are at the values of a typical subject.
[3] Determined by the LEAP™ imaging algorithm.

Conclusions

- This clinical trial simulation tool will help inform trial design, including inclusion/exclusion criteria, enrichment and stratification approaches for aMCI.
- The disease progression model is being coded into an R simulation package and web-simulator with a user-friendly graphical interface.
- Expansion of the modeling dataset with clinical trials data will also allow a description of placebo effect. FDA endorsement and EMA qualification are being pursued.

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