The Critical Path For Alzheimer's Disease: Hippocampal Volume as an Enrichment Biomarker in Trials of Patients with Mild Cognitive Impairment

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Background

- Hippocampal atrophy is associated with progression in Alzheimer disease (AD).
- The Critical Path for Alzheimer's Disease (CPAD) consortium is pursuing FDA qualification of baseline intracranial volume-adjusted hippocampal volume (ICV-HV) as an enrichment biomarker in clinical trials targeting mild cognitive impairment (MCI).

Objectives

- Evaluate the association between ICV-HV and disease progression using the Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB).
- Assess the enrichment utility of ICV-HV in MCI clinical trials.

Methods

Data

- Subject-level data from three sources – the 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 – yielded a total of 1,051 aMCI subjects with 7,860 CDR-SB timepoints in the screening-to-48 months interval.
- The statistical model used ADNI-1/-2 (N=702), and InDDEx was reserved for external validation.

Statistical Modeling

- The time course of Clinical Dementia Rating Scale, Sum of Boxes (CDR-SB) was described by a non-linear mixed-effects repeated measures model.
- Covariates were: baseline ICV-HV, sex, baseline mini-mental-state-examination (MMSE), baseline age, and apolipoprotein-E-encoding gene (*APOE*) genotype.
- ICV-HV enrichment was compared between two image analysis algorithms (LEAP™ and FreeSurfer™).

Clinical Trial Simulations

- Monte Carlo clinical trial simulations were performed to compare the statistical power by sample size in trials with(out) ICV-HV enrichment.
- Non-enriched trials included subjects sampled from the whole distribution of ICV-HV in the analysis dataset.
- Enriched trials sampled subjects from truncated ICV-HV distributions based on different cut-off values. A hypothetical drug effect of 50% reduction in progression rate was assumed.

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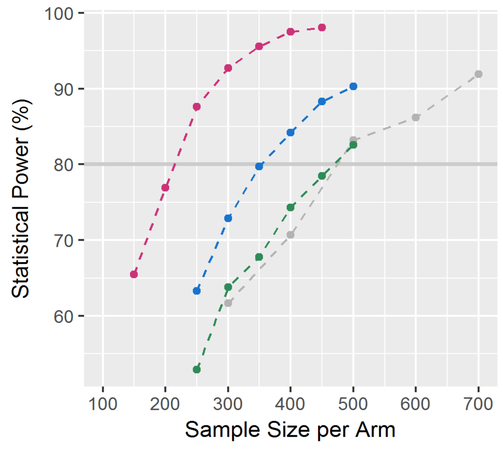
Results

- Separate covariate models, with ICV-HV values determined by LEAP™ or FreeSurfer™, were developed and assessed.
- After accounting for all covariates (sex, baseline age, baseline MMSE score, presence of APOE-ε4 allele), a 1cm³ decrease in baseline ICV-HV was associated to more than 50% increase in CDR-SB progression rate.

LEAP™



FreeSurfer™

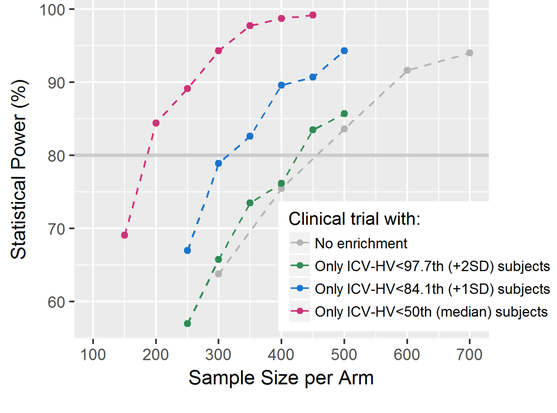


Figure 1 Statistical power *versus* sample size for simulated 24-month placebo-controlled parallel group ICV-HV-enriched and non-enriched clinical trials

ICV-HV thresholds for enrichment are illustrative. The simulations used: (a) the frequentist LEAP™ or 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: ICV-HV = intracranial volume-adjusted hippocampal volume, SD = standard deviation.

Results (continued)

Table 1 Sample sizes to achieve 80% power in simulated placebo-controlled parallel group with ICV-HV (non-)enriched trials

Clinical trials with:	Algorithm	Sample size for 80% power (95% CI*)	Sample size reduction of enriched *versus* non-enriched trials (%) (95% CI)
No enrichment	LEAP™	474 (468, 481)	Reference
Only ICV-HV<97.7th (+2SD) subjects	LEAP™	469 (459, 479)	1 (-1, 4)
Only ICV-HV<84.1th (+1SD) subjects	LEAP™	353 (338, 363)	26 (23, 28)
Only ICV-HV<50th (median) subjects	LEAP™	214 (210, 218)	55 (54, 56)
No enrichment	FreeSurfer™	456 (446, 465)	Reference
Only ICV-HV<97.7th (+2SD) subjects	FreeSurfer™	440 (431, 448)	3 (1, 6)
Only ICV-HV<84.1th (+1SD) subjects	FreeSurfer™	315 (300, 325)	31 (28, 34)
Only ICV-HV<50th (median) subjects	FreeSurfer™	186 (183, 188)	59 (58, 60)

Thresholds for enrichment are illustrative. The simulations used: (a) the frequentist LEAP™ or FreeSurfer™ covariate models; (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.

- The point estimates for the sample size reduction suggest that FreeSurfer™ yields a marginally higher sample size saving (2.2% to 5.4% higher) than LEAP™ (**Table 1**, last column). However, the difference in sample size savings by FreeSurfer™ *versus* LEAP™ was not statistically significant for one of the three enrichment scenarios (< +2 SD).

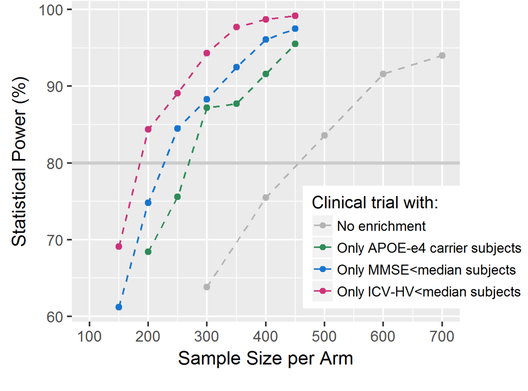


Figure 2 Statistical power *versus* sample size for simulated placebo-controlled parallel group enriched and non-enriched clinical trials

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.

Results (continued)

Recommendations for a New ICV-HV Algorithm with respect to its Enrichment Utility

- With technological advances, new ICV-HV algorithms will be introduced in the market. To determine whether the new algorithm provides greater or lower enrichment magnitude than LEAP™/FreeSurfer™ ('current algorithm'), one must analyze the new algorithm scores and subject-level clinical outcome data together.
- If a drug development sponsor does not have the resources/bandwidth to do such an analysis, a lower bound of the enrichment magnitude can be estimated based on the correlation between the ICV-HV values from the new and current algorithm. [Note that there was a linear relationship between ICV-HV values and intrinsic progression rate.]
- For the lower bound to be estimated, one must assume the worst-case scenario; i.e., the new algorithm is simply a noisy version of a current algorithm, where the noise is independent of the clinical outcome or the current algorithm. An algorithm that is noisier than the current algorithm would naturally have a reduced enrichment magnitude, in that an ICV-HV based-subject trial selection would be compromised.
- Under this assumption, new algorithms – where the ICV-HV values would correlate with those from LEAP™ ICV-HV by a Pearson's correlation coefficient of 0.9, 0.7, and 0.5 – would require sample size increases of approximately 7.5%, 23% and 49%, respectively (**Figure 3**).

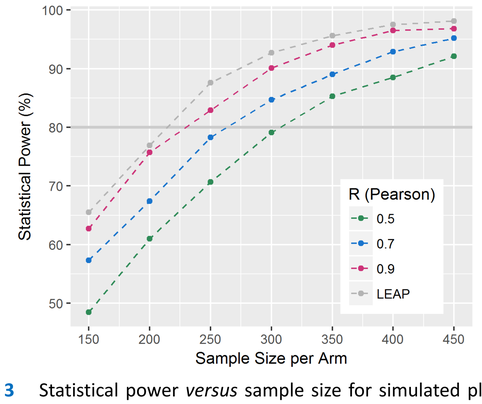


Figure 3 Statistical power *versus* sample size for simulated placebo-controlled parallel group ICV-HV enriched clinical trials

Enrichment scenarios are for LEAP™ ICV-HV, and hypothetical new ICV-HV algorithms whose ICV-HV values are correlated with LEAP™ ICV-HV [Pearson's correlation coefficient, R(Pearson), of 0.5, 0.7 or 0.9].

Conclusion

The use of baseline ICV-HV for clinical trial enrichment has the potential to greatly reduce trial size. These enrichment magnitudes are similar for FreeSurfer™ and LEAP™. Together with the baseline MMSE scores and the proportion of APOE-ε4 carriers, the most appropriate ICV-HV threshold can be selected based on the underlying model, in order to increase the likelihood of demonstrating drug effects in MCI clinical trials.