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 Som-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 (INDEEEx) 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-3/1-2 (N=702), and INDEEx 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 without ICV-HV enrichment.
• Enriched trials sampled subjects from truncated ICV-HV distributions based on different cut-off values. A hypothetical effect size of 50% reduction in progression rate was assumed.

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.

Table 1

<table>
<thead>
<tr>
<th>Clinical trials with</th>
<th>Algorithm</th>
<th>Sample size for 80% power (% (95% CI))</th>
<th>Sample size reduction of enriched versus non-enriched trials (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No enrichment</td>
<td>LEAP™</td>
<td>474 (468, 481)</td>
<td>Reference</td>
</tr>
<tr>
<td>Only ICV-HV&gt;214 (%)</td>
<td>LEAP™</td>
<td>469 (457, 481)</td>
<td>1 (1, 4)</td>
</tr>
<tr>
<td>Only ICV-HV&gt;210 (%)</td>
<td>LEAP™</td>
<td>353 (339, 363)</td>
<td>1 (1, 4)</td>
</tr>
<tr>
<td>No enrichment</td>
<td>FreeSurfer™</td>
<td>214 (210, 218)</td>
<td>55 (54, 56)</td>
</tr>
<tr>
<td>Only ICV-HV&gt;210 (%)</td>
<td>FreeSurfer™</td>
<td>456 (446, 465)</td>
<td>Reference</td>
</tr>
<tr>
<td>Only ICV-HV&gt;214 (%)</td>
<td>FreeSurfer™</td>
<td>440 (435, 445)</td>
<td>3 (1, 6)</td>
</tr>
<tr>
<td>Only ICV-HV&gt;212 (%)</td>
<td>FreeSurfer™</td>
<td>315 (303, 325)</td>
<td>1 (1, 6)</td>
</tr>
<tr>
<td>For enrichment</td>
<td>LEAP™</td>
<td>186 (183, 188)</td>
<td>59 (58, 60)</td>
</tr>
</tbody>
</table>

Thresholds for enrichment are illustrative. The simulations used: (a) the frequentist LEAP™ or FreeSurfer™ covariate model; (b) a hypothetical effect of 50% reduction in the disease progression rate; (c) the developed dropout model. No 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).

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—which 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).

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.

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 hypothetical drug effect of 50% reduction in the disease progression rate; (c) the developed dropout model. No simulations was 1,000 for each non-enriched or enriched scenario. AIC = Akaike Information Criterion; SD = standard deviation.

Figure 2

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

Enrichment scenarios are for LEAP™ ICV-HV, APOE, and MMSE. Thresholds for enrichment are illustrative. The simulations used: (a) the frequentist LEAP™ covariate model; (b) a hypothetical drug effect of 50% reduction in the disease progression rate; (c) the developed dropout model. No simulations was 1,000 for each non-enriched or enriched scenario. AIC = Akaike Information Criterion; ICC = Intraclass correlation coefficient; SD = standard deviation.

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 of 0.9, 0.7, or 0.5) would require sample size increases of approximately 7.5%, 23% and 49%, respectively (Figure 3).