## Supplementary Data

## Targeted Recruitment Using Cerebrospinal Fluid Biomarkers: Implications for Alzheimer's Disease Therapeutic Trials

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For a two-sample comparison of means, the required sample size is proportional to:

$$\frac{Var(X_1) + Var(X_0)}{\Delta^2}$$

where  $Var(X_1)$  and  $Var(X_0)$  denote the variance of the outcome measure in the treated and untreated groups respectively, and  $\Delta$  is the difference in mean outcome between treatment groups. Let  $X_{low}$ ,  $X_{high}$ , and  $X_{all}$ , denote the outcome in low-A $\beta$  level subjects, high-A $\beta$ level subjects, and all MCI subjects respectively. Further, let  $\Delta_{low}$  and  $\Delta_{all}$  denote the assumed treatment effects (difference in means) in a trial recruiting only low A $\beta$ -MCIs and all MCIs respectively.

<sup>1</sup>Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wpcontent/uploads/how\_to\_apply/ADNI\_Acknowledgement\_List.pdf We now derive the ratio of required sample sizes for a low-A $\beta$  targeted trial to the sample size for an all MCI trial, according to three alternative assumptions regarding the effect of a putative treatment:

a) if treatment reduces the mean outcome proportionately by 100k% in the low-A $\beta$  and by 100k% in the high-A $\beta$ , i.e.,  $\Delta_{low} = k\bar{X}_{low}$  and  $\Delta_{all} = k\bar{X}_{all}$ , the ratio is:

$$\frac{\frac{Var(X_{low}) + Var(X_{low})}{(k\bar{X}_{low})^2}}{\frac{Var(X_{all}) + Var(X_{all})}{(k\bar{X}_{av})^2}} = \frac{Var(X_{low})/\bar{X}_{low}^2}{Var(X_{all})/\bar{X}_{all}^2}$$

b) if treatment reduces mean outcome by an amount  $k\bar{X}_{low}$ , irrespective of whether A $\beta$  is high or low, i.e.  $\Delta_{low} = k\bar{X}_{low}$  and  $\Delta_{all} = k\bar{X}_{low}$ , the ratio is:

$$\frac{\frac{Var(X_{low}) + Var(X_{low})}{(k\bar{X}_{low})^2}}{\frac{Var(X_{all}) + Var(X_{all})}{(k\bar{X}_{low})^2}} = \frac{Var(X_{low})}{Var(X_{all})}$$

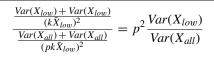
c) if treatment benefits low-A $\beta$  subjects only (by reducing mean outcome by  $k\bar{X}_{low}$ ) but not high-A $\beta$  subjects, i.e.,  $\Delta_{low} = k\bar{X}_{low}$  and  $\Delta_{all} = pk\bar{X}_{low}$ , where *p* denotes the proportion of low-A $\beta$  subjects, the ratio is:

<sup>&</sup>lt;sup>2</sup>Performed statistical analysis.

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| $\frac{Var(X_{low}) + Var(X_{low})}{(k\bar{X}_{low})^2}$  |
|---|
| $Var(X_{all}) + pVar(X_{low}) + (1-p)Var(X_{high}) + p(1-p)(\bar{X}_{high} - (1-k)\bar{X}_{low})^2$ |
| $(pk\bar{X}_{low})^2$   |

This ratio is always less than p, but unlike in scenarios a) and b), the ratio depends on k. However, for small k (i.e., small treatment effects) it is approximately equal to:



and hence again is independent of k.