Journal of Alzheimer's Disease 34 (2013) 1–2
IOS Press

Supplementary Data

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

Josephine Barnes[a,*], Jonathan W. Bartlett[a,b,2], Nick C. Fox[a], Jonathan M. Schott[a]
and for the Alzheimer's Disease Neuroimaging Initiative[1]
[a]*Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK*
[b]*Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK*

Accepted 8 November 2012

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 Δ is the difference in mean outcome between treatment groups. Let X_{low}, X_{high}, and X_{all}, denote the outcome in low-Aβ level subjects, high-Aβ level subjects, and all MCI subjects respectively. Further, let Δ_{low} and Δ_{all} denote the assumed treatment effects (difference in means) in a trial recruiting only low Aβ-MCIs and all MCIs respectively.

We now derive the ratio of required sample sizes for a low-Aβ 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-Aβ and by $100k\%$ in the high-Aβ, i.e., $\Delta_{low} = k\bar{X}_{low}$ and $\Delta_{all} = k\bar{X}_{all}$, the ratio is:

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

b) if treatment reduces mean outcome by an amount $k\bar{X}_{low}$, irrespective of whether Aβ 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-Aβ subjects only (by reducing mean outcome by $k\bar{X}_{low}$) but not high-Aβ subjects, i.e., $\Delta_{low} = k\bar{X}_{low}$ and $\Delta_{all} = pk\bar{X}_{low}$, where p denotes the proportion of low-Aβ subjects, the ratio is:

[1]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/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

[2]Performed statistical analysis.

*Correspondence to: Dr. Josephine Barnes, Dementia Research Centre, Box 16, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK. Tel.: +44 20 3448 3853; Fax: +44 20 7676 2066; E-mail: j.barnes@ucl.ac.uk.

ISSN 1387-2877/13/$27.50

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

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:

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

and hence again is independent of k.