Separate vs. simultaneous analysis of co-primary endpoints in Alzheimer's disease clinical trials

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Motivating example

Two highly correlated variables (0.9 residual error correlation) increase linearly with time (correlation 0.75 between slopes).
A 1% treatment effect on the slope of one of the variables is simulated. Two different analysis techniques are evaluated:

- one ignoring the covariance in random effects,
- the other accounting for it (the true model).

The power to detect the treatment effect is calculated for various sample sizes. The sample size needed for 80% power is decreased from 30 to 14 when accounting for covariance compared to ignoring it. Therefore it is of interest to investigate if this holds true in a more clinically relevant case.

Background and Objectives

In clinical trials of drugs intended for treatment of Alzheimer's Disease (AD), cognitive and functional measures may be used as co-primary endpoints. These variables are commonly evaluated in separate statistical tests. In theory, two endpoints measured simultaneously may have a joint distribution with respect to random effects. The power of detecting a treatment effect one or both of the endpoints may differ depending on if simultaneous or separate analyses are performed. The objective of this investigation was to calculate the power of finding a treatment effect on disease progression in a clinical AD trial comparing separate and simultaneous analysis of endpoints.

Methods

The ADNI database [1] was used for modeling. A dataset including ADAS-Cog 70 point total score and Functional Assessment Questionnaire (FAQ) was prepared. A mixed effects model (eq. 1) where subscript R indicates the different responses (ADAS-Cog and FAQ) was fitted to the data. A 30% treatment effect influencing the slope of the disease progression was simulated using the final model (eq. 2). Two cases were investigated:

1. Treatment effect on both ADAS-Cog and FAQ.
2. Treatment effect only on ADAS-Cog.

Datasets with 5000 subjects per arm (treatment/placebo) were simulated for both cases. Power calculations were performed using the MCMP method [2].

$$y_{Rij} = \beta_{1Ri}\left(1+\beta_{2Ri}x_{ij}\right)+\varepsilon_{Rij} \qquad \beta \sim MVN(\Theta,\Omega) \qquad \varepsilon \sim MVN(0,\Sigma) \qquad \text{(eq. 1)}$$

$$y=\beta_1\left(1+\beta_2(1-0.3^{TRT})\cdot x\right)+\varepsilon \qquad \text{(eq. 2)}$$

Results

The mixed effects model for ADAS-Cog and FAQ total scores fitted the data reasonably well with a tendency of overprediction at later assessments. The correlation between the base-line scores of ADAS-Cog and FAQ was estimated to 0.6 and the residual error correlation was estimated to 0.2.

For case 1), the required sample size for 80% power was similar for the simultaneous and separate analyses (n=115 vs. n=111). For case 2) the required sample size seemed to be marginally lower for simultaneous (n=187) compared to separate (n=203) analysis.

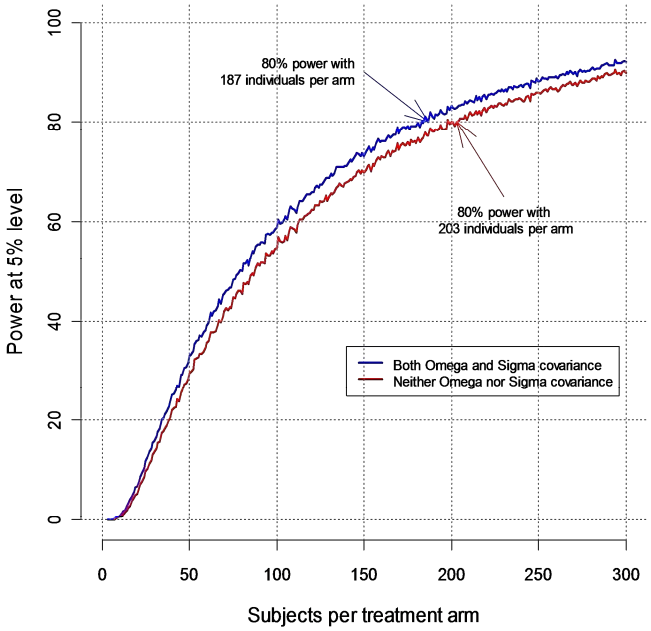

Figure: Power vs. sample size for the models with omega/sigma covariance included (blue line) or excluded (red line)

Discussion and conclusion

For this particular application, the difference with regards to power between simultaneous and separate analysis of endpoints was small. Generally, it is of interest to further investigate the influence of different degrees of random effects correlation on power for separate vs. simultaneous analysis. Furthermore, the influence of drop-out and model misspecification could be investigated for this particular case.

References

[1] Alzheimer's Disease Neuroimaging Initiative database http://adni.loni.ucla.edu/
[2] Camille Vong, Martin Bergstrand, Mats O. Karlsson Rapid sample size calculations for a defined likelihood ratio test-based power in mixed effects models PAGE 19 (2010) Abstr 1863 [www.page-meeting.org/?abstract=1863]

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