

PODE 2014

Population Optimum Design of Experiments: Workshop Roche, Basel, 11 September 2014

FIM Based Power Calculations for NLMEMs

Sebastian Ueckert

University of Uppsala, Sweden

Estimating the power of a future clinical study is a common problem in the drug development process. Within the framework of model based drug development this problem is solved through Monte-Carlo (MC) studies where numerous replicates of the trial are simulated and subsequently analysed. This process can be very time consuming due to the high number of replicates required to obtain a stable power estimate. Non-linear mixed effect models which are frequently used for the analysis of clinical trial data are especially problematic as they can have runtimes of several hours.

An alternative to time consuming MC studies are power calculations based on the Fisher information matrix. In this work three different information matrix based methods for power calculation were considered:

1. Wald statistic based power using a linear H_0 hypothesis
2. Wald statistic based power using a non-linear H_0 hypothesis
3. Parametric power estimation

All three methods were used to calculate the power to detect a drug effect in a hypothetical Alzheimer's trial based on a disease progression model from the literature. The obtained power versus samples size curves were compared to power values from a MC study.

The Wald statistic based power using a non-linear hypothesis as well as the parametric power estimation method were in good agreement with MC based power though slightly negatively biased. The Wald statistic using the linear the hypothesis, however, largely over-predicted the empirical power.

In conclusion, non-linear Wald and parametric power estimation are attractive alternatives to computationally intensive MC power studies.

References

Ueckert et al. *Optimizing disease progression study designs for drug effect discrimination*, JPKPD (2013) 40:587-596.

Ueckert et al. *Accelerating Monte-Carlo Power Studies through Parametric Power Estimation*, PAGE 23 (2014) Abstr 3263 [www.page-meeting.org/?abstract=3263]

Ito et al. *Disease progression model for cognitive deterioration from Alzheimer's disease neuroimaging initiative database*, Alzheimer's and Dementia (2011) 7:151-160.