Robust designs for longitudinal trials with binary data taking into account model uncertainty

JÉRÉMY SEURAT, FRANCE MENTRÉ AND THU THUY NGUYEN
IAME, INSERM, UMR 1137, University Paris Diderot, Paris, France

Abstract

Background/Objectives: Nonlinear mixed effect models (NLMEMs) are used in model-based drug development to analyze all longitudinal data obtained during clinical trials. Finding good design for these studies is important to get precise results and/or good power especially in case of sparse sampling. To design these studies, the expected Fisher Information Matrix (FIM) can be used. A method evaluating the FIM, without any linearization, based on Monte-Carlo and Hamiltonian Monte-Carlo (MC/HMC), has been proposed and implemented in the R package MIXFIM [1], which performs well with both continuous and discrete data. Nevertheless, this approach requires a priori knowledge of the model. We aim to propose and illustrate a robust approach based on MC/HMC to incorporate model uncertainty when designing a longitudinal study with repeated binary outcomes including two treatment groups.

Methods: To determine informative sampling times for a given model, different optimality criteria based on the FIM evaluated by MC/HMC can be computed, according to different purposes: the D-optimality to optimize the precision of the whole set of population parameters, the DS-optimality to accommodate situations in which only a subset of the model parameters is of interest (e.g. covariate effects), and the DDS-optimality to find a compromise between the D- and DS-optimality [2]. Then, uncertainty in model is taken into account using the compound D-, DS- and DDS-optimality to find informative designs which are robust across a set of candidate models. These methods are applied to design a longitudinal study in two treatment groups of 50 individuals. We consider four candidate NLMEMs for binary responses over time. Combinatorial optimization is performed to determine four informative sampling times, common to all these models. Using the expected FIM, we also predict the number of subjects needed to detect a significant treatment effect for each model with a power of 80%. The performance of the compound DDS-optimal design is evaluated by Clinical Trial Simulations (CTS) in terms of precision of parameter estimation and power of test to detect a treatment effect.

Results: Assuming uncertainty in candidate models lead to different optimal designs, and misspecification of models lead to designs with low efficiencies. The compound criteria provide robust CD-, CDS- and CDDS-optimal designs which are efficient across the four candidate models. In addition, the CDDS-optimal design allows a compromise between the overall precision of estimation and the power of test. The estimation error and the power predicted using the expected FIM for the finally proposed design are overall close to the values obtained by CTS.

Conclusions: The proposed design strategy based on MC/HMC and compound optimality theory, is a relevant approach which can be used to efficiently design longitudinal studies accounting for model uncertainty.

References:

[1] Riviere M-K, Ueckert S, Mentré F. An MCMC method for the evaluation of the Fisher information matrix for non-linear mixed effect models. *Biostatistics*. 2016; 17:73750.

[2] Atkinson A. C., Bogacka B. Compound D- and Ds-Optimum Designs for Determining the Order of a Chemical Reaction. *Technometrics*. 1997; 39:34756.