Project Title:

OPTIMUM DESIGNS FOR HETEROSCEDASTIC MODELS IN MULTI-ARM CLINICAL TRIALS

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Brief introduction

Most of the randomized clinical trials for treatment comparisons have been designed to achieve balanced allocation among the treatment groups in order to maximize the inferential precision in the estimation of the treatment effects. This is mainly due to the so-called "universal optimality" of balance, in particular in the context of the linear homoscedastic model. Indeed, it optimizes the usual design criteria for the estimation of the treatment contrasts, (like the well-known D-optimality minimizing the volume of the confidence ellipsoid of the contrasts, or the A-optimality minimizing the sum of the variances of the treatment effects estimators), and it is nearly optimal under several optimality criteria, also with heteroscedastic responses [1]. Considering the problem of testing statistical hypothesis about the treatment effects, balance is still optimal in the case of two treatments, as it maximizes the power of the test for normal homoscedastic responses and it is asymptotically optimal in the case of binary outcomes (see e.g. [2]). However, with several treatments the balanced allocation may not be efficient since it is different from the optimal design for hypothesis testing (see [3, 4]) and could be strongly ethically inappropriate for phase III-trials, in which the ethical demand of individual care could be of crucial importance.

Research question, aim, objectives

The main goal consists in designing randomized multi-arm clinical trials for treatment comparisons in order to achieve a suitable trade-off between inferential and ethical demands. The focus is on the appropriate balance of statistical precision - expressed by the power of the usual Wald test of homogeneity between the treatment effects (i.e., the classical *t*-test for the case of two treatments) - and ethical concerns related to the patients care.

1. We aim at considering heteroscedastic models taking into account uncensored and censored exponential responses, which are particularly relevant for oncological trials with survival endpoints, and binary trials.
2. Another interesting issue consists in including covariates/prognostic factors, to take also into account patients heterogeneity.
3. We intend to evaluate the operating characteristics of the multipurpose design methodology theoretically and by simulations in order to describe the performances of the proposal. Moreover, we aim at comparing the treatment allocation proportions maximizing the statistical power of the multivariate test of homogeneity of the treatment effects under a suitable ethical constraint with other designs suggested in the literature.
4. An additional goal is to apply standard Response Adaptive randomization procedures, namely, sequential allocation rules where at each step the patients are randomized according to suitable estimates of the unknown parameters in order to converge to the desired target (see e.g. the Efficient Randomized Adaptive Design in [5]).

The successful applicant is supposed to learn in depth the relevant aspects related to optimal design theory and sequential designs literature for comparative experiments, to find original solutions in line with the objectives of the research project previously described and implement them in Matlab or R software. The results will be presented at conferences and submitted for publication to relevant journals.

Participants in the study and the role they play

The successful applicant will be part of the STAT Department research group working on the design of experiments (Alessandro Baldi Antognini, Marco Novelli and Maroussa Zagoraiou). International partners and other researchers from the STAT Department with specific competencies (optimization methods, mathematical programming) could be involved in the project as well.

References

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3. Marco Novelli; Maroussa Zagoraiou, *Multipurpose optimal designs for hypothesis testing in normal response trials*, in: A. Abbruzzo, E. Brentari, M. Chiodi, D. Piacentino, Book of short Papers SIS 2018, Pearson, 2018, 1138 – 1143.

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5. Hu F, Zhang LX, He X. Efficient randomized-adaptive designs. The Annals of Statistics. 2009, 37, 2543-2560.