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PhD Thesis:	Adaptive clinical trials with multiple treatment arms.
Project title:	Integrated DEsign and AnaLysis of small population group trials.

Project description:

In this work we develop adaptive clinical trial designs to (i) perform efficient dose finding at an adaptive interim analysis and (ii) to confirmatory demonstrate efficacy using all accumulated data before and after an adaptive interim analysis. We investigate adaptive designs where both the interim and the final decision will be made either on a clinically relevant endpoint and/or appropriate surrogate endpoint(s).

For a better use of the available patient in small population groups, we assess how modelling and extrapolation can be incorporated in adaptive designs for confirmatory analysis. For the modelling part, we will extend methods for fixed sample designs such as the MCPMod [Bretz et al. 2005] to two stage adaptive designs [Bauer et al. 1999, Bretz et al. 2009] and develop confirmatory tests for the global trend assessment (i.e whether there is any statistical evidence for a dose-related drug effect) as well as for the pairwise comparison of the individual doses against placebo. In particular, modelling techniques as the MCPMod approach can be used to obtain model-based dose effect estimates at interim to guide early futility stopping and/or re-design the second stage (e.g. choice of doses, sample size, allocation ratio) and analysis (e.g., dropping

of inadequate response models).
By the means of clinical trials simulations we show the operating characteristics for specific adaptions rules. We suggest certain utility function, for which optimal adaptation strategies will be derived by backward induction.
We propose confirmatory model based testing strategies. To allow for uncertainty in the choice of the model, we will use Bayesian modelling averaging strategies to derive efficient and robust tests. The advantage
of such strategies is that if the model assumptions apply, it will allow for an unbiased efficient estimation of the full dose-response curve. On the other hand, even if the assumptions are violated, these model based tests will
still give a valid test to reject the overall null hypothesis of no treatment activity neither in doses or endpoints.
We will propose inference strategies, which rely on an aggregation of efficacy and safety endpoints from several treatment groups. We develop designs testing certain intersection hypotheses to proof efficacy and safety for the target population. E.g., instead of testing single doses separately, the efficacy test may rely on combing the efficacy information of certain dose groups together. Also instead of testing each single endpoint on its own, it might be more efficiently to combine the evidence of different endpoints.