# Adaptive Designs and Multiple Testing Procedures 2020

28th of May 2020
15:00 – 17:00 CET

Online Meeting: https://webconf.vc.dfn.de/admtp2020/
Passcode: IBS

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| **15:00-15:10** | **Welcome & Conference Information** |
| **15:10-15:45** | **Functional approaches for improving sample size recalculation in adaptive study designs**<br>Prof. Geraldine Rauch<br>Institute of Biometry and Clinical Epidemiology, Charité Berlin, DE |
| **15:45-16:20** | **Comparing Bayesian and frequentist group-sequential clinical trial designs**<br>Prof. Nigel Stallard<br>Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, UK |
| **16:20-17:00** | **Annual meeting of the ADMTP Working Group** |

## Functional approaches for improving sample size recalculation in adaptive study designs

Carolin Herrmann, Meinhard Kieser, Maximilian Pilz, **Geraldine Rauch**

Background: An adequate sample size calculation is essential for designing a successful clinical trial. One way to tackle planning difficulties regarding parameter assumptions required for sample size calculation is to adapt the sample size during the ongoing trial. This can be attained by adaptive group sequential study designs. At a predefined time point, the interim effect is tested for significance. Based on the interim test result, the trial is either stopped or continued with the possibility of a sample size recalculation. There exists a number of such sample size recalculation rules. However, these rules have different limitations in application like a high variability of the recalculated sample size or the problem that the target power is not met.

Methods: Sample size recalculation rules can be interpreted as functions in the observed interim effect. All recalculation rules have in common that they take values between 0 (no additional sample size) and a predefined maximal sample size. The questions is thus, what the optimal shape of such a curve is. Often, a single “jump" from 0 to the maximal sample size is implemented and the curve decreases monotonously afterwards. This jump is one reason for a high variability of the sample size. In this work, we investigate how the shape of the recalculation function can be optimized by implementing a smoother increase of the sample size on the one hand and by an optimized shape of the monotonously decreasing function on the other hand. We propose two approaches to improve sample size recalculation rules: a) We consider smoothing corrections to allow a smooth sample sizes increase; b) We examine a polynomial function modelling the sample size decrease with a parameter choice based on pre-defined performance criteria. The design options are evaluated by means of Monte Carlo simulations. Evaluation criteria are univariate performance measures such that the average conditional power and the average sample size as well as a conditional performance score which incorporates sample size and power components.

Conclusions: Based on the simulation study, we present easily implemented elements and methods to improve sample size recalculation rules for normally distributed endpoints in two-stage adaptive group sequential study designs. The approaches can be combined or partly adapted to the existing rules described in the literature.

## Comparing Bayesian and frequentist group-sequential clinical trial designs

**Nigel Stallard**, Susan Todd, Elizabeth Ryan, Simon Gates

Group-sequential designs enable interim analyses to be performed during a clinical trial with the trial stopped as soon as sufficient evidence of efficacy or futility has been observed. Both frequentist and Bayesian group-sequential methods have been proposed. In the former, an alpha-spending function may be used to construct stopping boundaries that control the overall type I error rate, whereas in the latter, stopping boundaries are based on the posterior distribution of the treatment effect given the observed data. A recent development has been the proposal to set Bayesian designs to control the frequentist type I error. This talk will compare designs obtained using spending function and Bayesian methods that control the type I error rate.

The Bayesi an approach for a two-arm trial can be formulated in two ways, either with a prior specified directly for the difference between experimental and control treatments or with effects for the two treatment having independent prior distributions. In the one-parameter setting frequentist and Bayesian group-sequential designs can be identical if sufficient flexibility in choice of design parameters is allowed, and we show that frequentist and Bayesian group-sequential designs may be very similar for common choices of stopping rules. In the two-parameter setting we show that the frequentist and Bayesian designs cannot correspond, and that Bayesian group-sequential designs cannot generally control the type I error rate for all values of the control treatment effect.