

## **Kolloquium „Statistische Methoden in der empirischen Forschung“**

Wann: 12. Dezember 2017, 17:00 – 18:30 Uhr

Wo: Robert Koch-Institut | Nordufer 20 | 13353 Berlin (Wedding),  
S41, S42, U9 Westhafen | U9, Bus 142 Amrumer Str

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### **Optimized Rules and Performance Criteria for Adaptive Designs with Sample Size Recalculation**

#### **Introduction**

In standard clinical trial designs, the required sample size is fixed in the planning stage based on initial parameter assumptions. It is intuitive that the correct choice of sample size is of major importance for an ethical justification of the trial and a responsible spending of resources. In an underpowered trial, the research hypothesis is unlikely to be proven, resources are wasted and patients are unnecessarily exposed to the study-specific risks. If the sample size is too large, the market approval is prolonged and later recruited patient in the control arm are exposed to a treatment already known to be less effective.

The parameter assumptions required for sample size calculation should be based on previously published results from the literature and on aspects of clinical relevance. In clinical practice, however, historical studies for the research topic of interest are often not directly comparable to the current situation under investigation or simply do not exist. Moreover, the results of previous studies often show a high variability or are even contradictory.

Calculating the ‘correct’ sample size is thus a difficult task. On the other side, the consequences of a ‘wrong’ sample size are severe. Adaptive group sequential designs allow a sample size recalculation after a planned unblinded interim analysis in order to adjust the trial sample size during the ongoing trial. Most often, the sample size recalculation within an adaptive design is based on conditional power arguments using an updated estimate of the treatment effect.

#### **Methods**

The global aim is to provide methods which enable a more effective planning of medical research projects in the future by means of adaptive sample size recalculation designs with good performance properties. To do so, there exist two separate main challenges: The first challenge is to establish sensible criteria for ‘good’ performance. The second challenge is the development of new adaptive sample size recalculation rules which overcome the existing problems and which show good performance properties.

#### **Results**

Our results confirm that the standard approach to recalculate the required sample size based on the conditional power of the observed effect at interim has major shortcoming.

We illustrate and discuss the reasons for the bad performance of this approach and present new performance criteria that should be investigated to judge an adaptive design. Moreover, we present first results of a new approach for a potential better sample size recalculation.

### **Discussion**

Although adaptive group sequential designs seem to be an elegant option to overcome uncertainties in the planning stage the actual gains of these designs can often be questioned.

This talk contributes new aspects on the quantification of a good performance and discusses approaches to develop better recalculation strategies.