MEDICAL UNIVERSITY OF VIENNA

Wiener Biometrische Sektion
Der Internationalen Biometrischen Gesellschaft
Region Österreich –Schweiz

Einladung zum Biometrischen Kolloquium

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GROUP SEQUENTIAL ADAPTIVE DESIGNS IN A SERIES OF TIME-TO-EVENT RANDOMIZED TRIALS IN RARE DISEASES: A SIMULTAION STUDY

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Abstract:

In rare diseases, fully powered large trials may not be doable in a reasonable time frame even with international collaborations. In a previous work, we proposed an approach based on a series of smaller parallel group two-arm randomized controlled trials (RCT) performed over a long research horizon (Bayar et al., 2016). Within the series of trials the treatment selected after each trial becomes the control treatment of the next one. We concluded that running more trials with smaller sample sizes and relaxed α-levels leads in the long term and under reasonable assumptions to larger survival benefits with a moderate increase of risk as compared to traditional designs based on larger but fewer trials designed to meet stringent evidence criteria.

We now extend this quantitative framework with more `flexible' designs including interim analyses for futility and/or efficacy, and three-arm adaptive designs with treatment selection at interim. In the simulation study we considered different disease severities, accrual rates, and hypotheses of how treatments improve over time. For each design we estimated the long-term survival benefit as the relative difference in hazard rates between the end and the start of the research horizon, and the risk defined as the probability of selecting at the end of the research horizon a treatment inferior to the initial control. We assessed the impact of the α-level and the choice of the stopping rule on the operating characteristics. We also compared the performance of series based on two- vs. three-arm trials.

We show that relaxing α-levels within the limit of 0.1 is associated with larger survival gains and moderate increase of risk which remains within acceptable ranges. Including an interim analysis with a futility rule is associated with an additional survival gain and a better risk control as compared to series with no interim analysis, when the α-level is below or equal to 0.1, whereas the benefit of including an interim analysis is rather small for higher α-levels. Including an interim analysis for efficacy yields almost no additional gain. Series based on three-arm trials are associated with a systematic improvement in terms of survival gain and risk control as compared to series of two-arm trials.