Exploring the benefits of adaptive sequential designs in time-to-event endpoint settings

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Sequential analysis is frequently employed to address ethical and financial issues in clinical trials. Sequential analysis may be performed using standard group sequential designs, or more recently, adaptive designs with data-driven modification of sample sizes. In the general setting, it is unclear whether there is any advantage to adaptive designs over traditional group sequential designs, but in survival analysis with a time-to-event endpoint there may be a benefit in being able to stop subject accrual earlier. As accrual of subjects is often an expensive procedure, an adaptive design that reduces the maximal possible sample size at an early stage of the trial—and thus allows early termination of accrual—may reduce the costs associated with the trial. We consider a family of adaptive designs that allow sample size readjustment based on the results of the first interim analysis, and we match each adaptive design to a standard group sequential design that has an equivalent power function. We investigate and compare the trade-offs between efficiency (as measured by number of observed events required) and cost (a function of the number of subjects accrued and length of observation) for a variety of patient accrual and trial cost scenarios. In particular, we consider the relative contribution of per-patient costs and the calendar time costs of financing the drug development process.