OPERATING-CHARACTERISTIC GUIDED DESIGN OF GROUP-SEQUENTIAL TRIALS

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Abstract. Group-sequential designs are commonly used for clinical trials to allow early stopping for efficacy or futility. While the design of a single-stage randomized trial is guided by a target power for an alternative hypothesis of interest, the addition of interim analyses is driven by technical choices that are less understandable for clinicians. For example, the commonly used Lan-DeMets methodology requires specification of the timing of analyses and error spending functions. Since the rationale and effect of these technical choices is often unclear, the operating characteristics of the final design are explored under various values of the parameter of interest, and the design is then adjusted until desired properties are obtained.

In this work we develop methods for constructing designs that achieve the desired operating characteristics without the need to specify error spending functions or the timing of analyses. Specifically, we consider designing a study for the mean difference δ of a normally distributed outcome with known variance. The null hypothesis $H_0 : \delta = \delta_0$ is tested versus $H_a : \delta = \delta_A$, with power π at a significance level α. The interim analyses are designed so that for a pre-specified sequence δ_{Ak} the study stops for efficacy at stage k with probability π if $\delta = \delta_{Ak}$. If stopping for futility is also considered, then the requirement to stop for futility at stage k with probability π_F if $\delta = \delta_{0k}$ for pre-specified sequence δ_{0k} can also be added. We show that under some monotonicity restrictions, such designs exist for any choice of the timing of interim analyses. Specific designs can be selected by imposing additional optimality requirements, such as minimizing the expected sample size under the target alternative δ_A, or the average sample size under a weighted selection of the alternatives.

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