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Conditional Power and Model Selection Based Sample Size Reestimation with Type I Error Recalibration

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INTRODUCTION

The sample size estimation at study design depends on initial assumptions regarding the target power, treatment effect, accrual/follow-up duration and the underlying exponential distribution for time-to-event outcomes. However, observed data often deviate from these assumptions and the study may not progress as planned. Obtaining an updated sample size estimation after study initiation represents a valuable resource for monitoring, statistics and ethical considerations.

OBJECTIVES

We introduce a methodological framework for sample size reestimation at interim stages of clinical trials with time-to-event endpoints using conditional power (CP) and model selection procedures. We developed an R function to compute the updated sample size and to recalibrate the type I error rate, based on the number of events required to achieve the target CP and the number of events observed at interim.

METHODS

The input data include design-stage parameters (type I error rate, hazard ratio, follow-up duration, target number of events and power), subject-level information (identifier, treatment arm, enrollment date, event status, event date, date of last observation), and user-defined updates (extended accrual and/or follow-up). Subjects are categorized by their follow-up status: lost to follow-up, event-free at the interim stage, or having experienced the event of interest. Time-to-event is computed in days for each subject and four parametric models (exponential, Weibull, log-normal and log-logistic) are fitted for each treatment group and compared using the Akaike Information Criterion (AIC) to identify the optimal arm-specific fits. Following the standardization of the chi-square statistic from the log-rank test, the interim CP is computed with Jennison and Turnbull's equation [1]. The lower boundary of the interim CP acceptance region is derived using the Broberg's methodology [2]. If the observed CP is below this boundary, the function flags potential study futility and no sample size is updated. In the event the interim CP is greater than or equal to the target CP, the function confirms that the study is progressing as planned and the sample size remains unchanged. When the interim CP falls within the region, the required number of events to achieve the target CP is computed using the Newton–Raphson algorithm, the updated sample size is estimated via a generalized Schoenfeld formula based on Lachin and Foulkes' framework and the type I error rate recalibration is performed using the technique proposed by Uemura, Matsuyama and Ohashi [3] [4] [5].

RESULTS

We applied our method at an interim stage of a phase III trial that evaluates the superiority in terms of Progression Free Survival (PFS) of an experimental treatment versus the control in metastatic colorectal cancer subjects. Starting from a hazard ratio of 0.58, a one-sided type I error of 5%, one-year follow-up and a planned enrollment of 140 subjects to observe 106 PFS events with a 80% target power, we updated the sample size and recalibrated the type I error assuming one additional year of accrual. At the interim analysis (three years after trial initiation), 18 PFS events and 44 enrolled subjects corresponded to an interim CP of 50.9%. For the experimental group, the exponential distribution provided the optimal fit for the time-to-event data, whereas the log-normal was identified as the best model for the control group. To achieve the target

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CP of 80%, the function increased the sample size to 269 subjects to observe 154 events. Consequently, the recalibrated one-sided type I error rate decreased to 3.1%, consistent with the slow accrual and low event rates observed at interim.

CONCLUSIONS

This method enhances the clinical trials management effectively by providing the updated sample size at interim stages of clinical trials in a timely and methodologically sound manner. This function supports the operational and statistical aspects of clinical trials, contributing to their overall success.

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