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%PT_GSDesign: A SAS Macro for Group Sequential Designs with Time-to-event Data using the Concept of Proportional Time

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Summary

Treatments that are found to be promising in a Phase II trial are studied more comprehensively in a Phase III trial where researchers aim to investigate the effectiveness and safety of the new treatment against the current standard-of-care. While traditional approaches require the calculation of a fixed sample size depending on the type I error, power and clinically important treatment effect, in the medical setting they suffer from the limitation that patients are continually being accrued into a study based on the accrual rate, the availability of qualified patients (based on inclusion/exclusion criteria) and the possibility of random dropouts among many factors. Thus, the primary outcome of interest is not available simultaneously on all patients and researchers may be interested to look at outcomes on the early enrollees and use that as a basis to decide whether the trial should be continued. Sequential testing in large-sized Phase III trials with interim points can be used to - {i} stop the trial early for overwhelming evidence of efficacy, {ii} stop the trial early for overwhelming evidence for futility, and {iii} continue the trial for lack of evidence of efficacy or futility.

A Group Sequential Design (GSD) formalizes the concept by providing a statistical framework under which either of the three decisions can be taken after looking at interim results. Ethical, financial and administrative requirements often guide the statistical designs of GSDs (see Enas et al. (1989); Jennison & Turnbull (1990); Ellenberg et al. (2002)). Such GSDs have been well developed for continuous and binary outcomes and have a long history starting with quality control applications (Wald (1947)) and progressing to the medical setting (Armitage (1960)). Vast literature is available on this topic in many books (Whitehead (1997); Jennison & Turnbull (2000); Proschan et al. (2006); Dmitrienko et al. (2005); Wassmer & Brannath (2016)) and overview articles (Whitehead (1999); Todd (2007); Mazumdar & Bang (2008)). When dealing with time-to-event outcome, a repeated significance testing approach incorporating a family of designs (Pocock (1977); O'Brien & Fleming (1979); Wang & Tsiatis (1987)) can be combined with the error spending method (Lan & DeMets (1983)) to implement a GSD using a log-rank test or by using the proportional hazards (PH) assumption. Popular statistical software such as GPower, PASS, and nQuery often implement GSDs for time-to-event outcome using the weighted and unweighted versions of the log-rank test either explicitly assuming exponentially distributed survival times or with the PH assumption and are able to incorporate complexities of survival outcomes such as random dropouts, prespecified accrual and follow-up times, varying accrual patterns, equal/unequal spaced interim testing points (looks), efficacy-only designs, efficacy and futility designs, binding and non-binding futility rules, and many other flexible features specific to time-to-event outcomes.

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Statement of need

When the underlying assumptions that drive the analytical and simulation-based approaches using the framework of the log-rank test are not valid, hardly any alternate methods are available in literature or in standard statistical software. Recent developments in this field have considered relaxing the PH assumption in favor of a 'proportionality of time (PT)' assumption leading to development of GSDs in the context of an accelerated failure time (AFT) model (Phadnis & Mayo (2020)). The authors have described various scenarios in the biomedical setting where their approach could be advantageous compared to the standard methods with the help of real-life examples. Their proposed GSD method provides an alternate approach when the PH assumption is not appropriate and allows various hazard shapes (increasing/decreasing monotonically over time, bathtub shaped, arc-shaped) using the generalized gamma distribution. The purpose of this paper is to present a fully functional SAS macro that can be used to implement their GSD method (SAS Institute Inc (2010)). The SAS macro incorporates multitude of design features specific to a two-arm GSD for time-to-event outcomes and includes validation for any parameters defined by the user, as well as suggestions for correcting erroneous input.

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