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Title: Design and Analysis of Clinical Trials with Restricted Mean Survival Time

Abstract: Restricted mean survival time (RMST), a summary of survival time up to a pre-specified clinically relevant truncation time, is increasingly recognized as a measure for treatment effect in recent biomedical studies with time-to-event endpoints. The difference or ratio of RMST between two groups (e.g., treatment versus control) measures the relative treatment effect concerning a gain or loss of survival time. The RMST offers greater flexibility compared to the hazard ratio (HR), which is often estimated from the Cox proportional hazards model under the proportional hazards (PH) assumption. Due to delayed treatment effects or other biomedical reasons, the PH assumption is often violated in oncology and cardiovascular trials, leading to biased estimation and misleading interpretations of treatment effects. Compared to HR, RMST requires no PH assumption and offers a more straightforward interpretation of treatment effects.

In this dissertation, we propose novel RMST-based methodologies for clinical trials with time-to-event endpoints in three research areas:

1) ***Individual participant-level meta-analysis.*** Network meta-analysis (NMA) compares multiple treatments simultaneously by combining direct and indirect comparisons. Individual participant data (IPD) allow for evaluating treatment effect moderation by taking full utilization of individual covariates from multiple clinical trials. In IPD-NMA, RMST models have gained popularity, but current approaches lack the proper incorporation of individual covariates. We propose advanced models to estimate RMSTs with covariate adjustment and their interaction effects in IPD-NMA. The methods are illustrated using a real NMA example for patients with atrial fibrillation.

2) ***Inference in multiple-regional clinical trials.*** Multi-regional clinical trials (MRCTs) are increasingly pivotal in global pharmaceutical development. Existing methods have ignored the difference in baseline characteristics of study participants across regions, resulting in biased treatment effect assessment. Moreover, limited attention has been given to time-to-event outcomes. We propose inference methods for assessing regional treatment effect heterogeneity with consideration for eliminating regional imbalance due to extrinsic regional factors. Theoretical work is employed to establish the large sample properties of the proposed methods. The methods are compared through extensive simulation studies and illustrated using a real MRCT on acute coronary syndromes.
3) ***Biomarker-guided adaptive and enrichment design.*** Biomarker-guided designs are increasingly used to evaluate personalized treatments in Phase II and III clinical trials. With adaptive enrichment, these designs improve the efficiency of clinical trials by reducing the number of randomized patients while increasing the proportion of biomarker-positive patients. However, limited research exists on biomarker-guided adaptive enrichment trials with time-to-event endpoints. In this study, we propose a novel multi-stage biomarker-guided adaptive RMST design with threshold detection for biomarker positives and patient enrichment. We develop sophisticated methods for type I error control and treatment effect estimation for biomarker positive patients.