Randomized Optimal Selection Design for Dose Optimization

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ABSTRACT

The U.S. Food and Drug Administration (FDA) launched Project Optimus to shift the objective of dose selection from the maximum tolerated dose to the optimal biological dose (OBD), optimizing the benefit-risk tradeoff. One approach recommended by the FDA's guidance is to conduct randomized trials comparing multiple doses. In this paper, using the selection design framework, we propose a randomized optimal selection (ROSE) design, which minimizes sample size while ensuring the probability of correct selection of the OBD at prespecified accuracy levels. The ROSE design is simple to implement, involving a straightforward comparison of the difference in response rates between two dose arms against a predetermined decision boundary. We further consider a two-stage ROSE design that allows for early selection of the OBD at the interim when there is sufficient evidence, further reducing the sample size. Simulation studies demonstrate that the ROSE design exhibits desirable operating characteristics in correctly identifying the OBD. A sample size of 15 to 40 patients per dosage arm typically results in a percentage of correct selection of the optimal dose ranging from 60% to 70%. A user-friendly software for implementing ROSE designs is available on www.trialdesign.org.

Keywords: Dose optimization; Optimal design; Randomization; Selection design.

Exploring Sensitive Biomarkers with Short-Term Response and Long-Term Outcome Using Bayesian Additive Regression Trees

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ABSTRACT

Identifying good predictive baseline covariates for optimizing the target population for a new treatment is a topic that has attracted great interest. In some situations, an early post-baseline biomarker response may serve as a supportive guide for physicians to decide whether to continue a treatment for a patient. We propose an exploratory two-stage subgroup-analysis method as a statistical tool to investigate a role of such a short-term outcome in informing each individual patient of whether they benefit from a new treatment in terms of long-term outcome. We use a flexible probability model, Bayesian additive regression trees (BART), to derive predictive conditional treatment effects (PCTE) in a short-term post-baseline biomarker response based on counter-factual modeling of responses to new and standard treatments for each patient. Constructing patient subgroups according to the PCTE values, we analyze an observed long-term outcome to explore a sensitive subpopulation. We carry out extensive simulation studies to examine the operating characteristics of the proposed method. For illustration, we apply the proposed method to data from a randomized clinical trial in oncology.

Keywords: Bayesian additive regression trees; Short-term biomarker response; Time-to-event; Sensitive subpopulation; Randomized clinical trials.

BIT: A Bayesian Optimal Adaptive Clinical Trial Design for Integrated Therapies

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ABSTRACT

Complex chronic diseases often require integrated therapies administered sequentially across different disease phases. In alcohol-associated hepatitis (AH) and alcohol use disorder (AUD), optimizing treatment selection is essential for improving long-term survival. In this talk, we introduce a Bayesian adaptive design specifically tailored for integrated therapy trials (BIT). The BIT design employs flexible Bayesian parametric modelling approaches to characterize therapeutic effects across disease phases and incorporates multiple interim analyses with adaptive stopping rules for both futility and superiority to enhance efficiency while strictly controlling the family-wise type I error rate and maximizing statistical power. Simulation studies confirm the desirable operating characteristics of the BIT design. While motivated by AH/AUD, the proposed framework is broadly applicable to other complex chronic diseases requiring sequential treatment strategies.

Keywords: Adaptive design, Bayesian statistics, Clinical trial