An Adaptive Trial Design to Optimize Dose--Schedule Regimes with Delayed Outcomes

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Abstract: We propose a two-stage phase I-II clinical trial design to optimize dose--schedule regimes of an experimental agent within ordered disease subgroups in terms of toxicity--efficacy tradeoff. The design is motivated by settings where prior biological information indicates it is certain that efficacy will improve with ordinal subgroup level. We formulate a flexible Bayesian hierarchical model to account for associations among subgroups and regimes, and to characterize ordered subgroup effects. Sequentially adaptive decision making is complicated by the problem, arising from the motivating application, that efficacy is scored on day 90 and toxicity is evaluated within 30 days from the start of therapy, while the patient accrual rate is fast relative to these outcome evaluation intervals. To deal with this in a practical way, we take a likelihood-based approach that treats unobserved toxicity and efficacy outcomes as missing values, and use elicited utilities that quantify the efficacy-toxicity trade-off as a decision criterion. Adaptive randomization is used to assign patients to regimes while accounting for subgroups, with randomization probabilities depending on the posterior predictive distributions of utilities. A simulation study is presented to evaluate the design's performance under a variety of scenarios, and to assess its sensitivity to the amount of missing data, the prior, and model misspecification.