The influence of particular design elements on operational characteristics of trials using Bayesian biomarker-driven outcome-adaptive randomization

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Abstract

Bayesian biomarker-driven outcome-adaptive randomization (OAR) designs have drawn a lot of attention in, e.g., cancer clinical trials. They extend traditional fixed-randomization-ratio designs by allowing the ratio to change continuously, within the strata defined by biomarker values, based on the collected outcome information. It has been advocated that the adaptation allows simultaneous identification of predictive markers and marker-specific treatments. Despite increasing use of these designs, questions regarding their implementation and operational characteristics are still asked.

As an example, we consider a design proposed by Barry et al. (2015). It applies an hierarchical probit model to estimate efficacy of two treatments in two biomarker-strata using a binary clinical outcome. The design is characterised by a stopping rule with irreversible suspension of accrual to inefficacious treatment-stratum combinations. OAR is initiated after an initial series of $n_0 = 25$ patients randomized according to the 1:1 randomization ratio.

In the aforementioned design, one may have to make several decisions regarding: criteria for testing futility and efficacy of treatments; the timing of the start of OAR; prior distributions to be used; the particularities of Bayesian estimation such as selecting number of burn-in and posterior iterations, convergence monitoring, and dealing with non-convergence if it occurs. We are interested in the influence of the different choices on the operational characteristics of the trial.

It appears that the choices may have important and sometimes unexpected consequences. For instance, using different thresholds for the treatment effect in criteria for testing of futility and efficacy may lead to counterintuitive results in terms of the sample size requirements for the trial. Care is needed when deciding about the number of MCMC sampling iterations used in the Bayesian estimation algorithm, because for some of the parameters of the hierarchical model an unexpectedly large number of iterations may be required. Obviously, specification of prior distributions requires thought, because some choices may lead to excessive of “borrowing” of information about treatment effect across strata, causing bias in conclusions regarding efficacy and/or futility. In our paper, we illustrate and discuss consequences of these and other choices regarding the design of a Bayesian biomarker-driven OAR trial.