Implementing optimal designs for dose-response studies through adaptive randomization for a small population group

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Abstract

In dose-response studies with censored time-to-event outcomes, D-optimal designs depend on the true model parameters and on the amount of censoring in the model. In practice, such designs can be implemented adaptively, by performing dose assignments according to updated knowledge of the dose-response curve at interim analysis. It is also essential that treatment allocation involves randomization to mitigate various experimental biases and enable valid statistical inference at the end of the trial.

In this work we perform a comparison of several adaptive randomization procedures that can be used for implementing D-optimal designs for dose-response studies with time-to-event outcomes with small to moderate sample sizes. The operating characteristics of randomization procedures involve measures of treatment allocation balance, randomness of treatment assignments, variations in the allocation ratio, and statistical characteristics such as type I error rate, power, and estimation efficiency. For a small sample size, the commonly used completely randomized design (CRD) results in higher variance of model parameters' estimation and less power compared to the procedures targeting optimal allocation proportions. The results of the current work should help clinical investigators select an appropriate randomization procedure for their dose-response study. We also present a web-based R shiny application that can be used to reproduce all results in this presentation and perform additional simulations for user-defined experimental scenarios.

Keywords: D-optimal design, Dose-response study, Randomization, Time-to-event outcomes, Unequal allocation.