D-optimal designs for dose finding in phase I clinical trials

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ABSTRACT

Determining the maximum tolerated dose (MTD) is the main challenge of phase I clinical trials. There are many methods in the literature to determine the MTD. The D-optimal design can also be used to find the MTD. The D-optimal design depends on the Fisher information matrix (FIM), and it minimizes the generalized variance of the parameter estimates. However, the D-optimal design is yet to receive much attention from clinicians. Since a dose-response model is usually non-linear, the FIM depends on the unknown model parameters. To optimize the FIM through the D-criterion, values need to be assumed for the model parameters. This paper's focus is to investigate four different D-optimal designs depending on parameter values: design based on posterior Bayes estimators, design based on maximum likelihood estimators, sequential Bayesian design, and two-stage Bayesian design. Six plausible dose-response scenarios are investigated through a simulation study. Except for the design that utilizes maximum likelihood estimates in the optimization of FIM, all other designs are found very competitive for the correct MTD recommendation. Because of its numerical simplicity compared to the others, the posterior-based D-optimal design is recommended for dose-finding in phase I clinical trials.

Key words: Phase I clinical trials, maximum tolerated dose, adaptive design, D-optimal design, Bayesian D-optimal design.