Journal of Statistical Planning and Inference 177 (2016) 64–73

Contents lists available at ScienceDirect

Journal of Statistical Planning and Inference

journal homepage: www.elsevier.com/locate/jspi

Sequential design for binary dose–response experiments

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ARTICLE INFO

Article history:
Received 17 November 2015
Received in revised form 14 April 2016
Accepted 19 April 2016
Available online 3 May 2016

Keywords:
Clinical trial
Dose–response experiment
Optimal design
Sequential
Two-stage design
Up-and-down design

ABSTRACT

In dose–response studies, experiments are often carried out according to optimal designs for the purpose of accurately determining a specific effective dose (ED) level. If the interest is in the dose–response relationship over a range of ED levels, the existing optimal designs is misaligned. In this paper, we propose a two-stage sequential ED-design for this purpose. We use a small number of trials to provide a tentative estimation of the parameters. The dose levels of the subsequent trials are then selected sequentially, based on the latest model information, to maximize the efficiency of the ED estimation over several ED levels. Simulations indicate that the proposed design compares favorably with existing designs under various scenarios.

1. Introduction

Dose–response experiments are routinely conducted in Phase I and II clinical trials to study the relationship between the doses of a stimulus and the responses of experimental subjects. Estimating the underlying dose–response relationship is the primary goal of dose–response experiments (Dette et al., 2005; Dragalin et al., 2008). In medicine, it is crucial to have thorough knowledge of the effective and safe dose range of a medication. The dose given to a patient must be high enough to induce the desired response and low enough to avoid potential adverse effects. For example, anesthesiologists must know the dose range that will anesthetize patients without harming them. The characterization of the dose–response relationship is therefore an important element in the pharmacodynamic description of anesthetic drugs. The information is vital in guiding the selection of the dose levels used in local, intravenous, inhaled, and repeated anesthetics (Pace and Stylianou, 2007).

Accurately charactering the dose–response relationship is also a key step in the clinical development process of pharmaceutical drugs. Poor understanding of the underlying dose–response relationship often results in selecting wrong target doses to be used in large scale confirmatory clinical trials, which may cause serious ethical and financial consequences. Selecting too high a dose may cause potential toxicity to experimental subjects, and choosing too low a dose may fail to establishing adequate efficacy, and fail to obtain the regulatory approval of the drug (Dette et al., 2008; Bretz et al., 2010). We refer to Ting (2006) and Bretz et al. (2008) on dose–response experiments in drug development process for some general discussion on issues and challenges.

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http://dx.doi.org/10.1016/j.jspi.2016.04.005
0378-3758/

The dose–response relationship also plays a vital role in other ventures. For instance, in pyrotechnics applications, it is important to know the sensitivity of a new explosive to the stress of a shock; see Dror and Steinberg (2008) and Wu and Tian (2013).

If the dose–response relationship were known, we could find the design that gives the most efficient estimation of the model parameters (Wu, 1985; Ford et al., 1985; Sitter and Wu, 1993; Sitter and Fainaru, 1997; Sitter and Forbes, 1997). A practical approach is to first run a pilot study in which the dose levels are based on prior knowledge. The resulting data will provide an improve estimate of the model parameters. The optimal design based on the fitted model is then used for further trials. A full sequential approach can also be used: the parameter estimates are updated after each stage of the experiment and used to determine appropriate dose levels for the subsequent trials.

Another popular design that addresses ethical and safety concerns is the up-and-down method (Anderson et al., 1946; Von Békésy, 1947; Dixon and Mood, 1948). In this design, the dose of the next trial is one level higher or lower than that of the current trial depending on the outcome of the current response. Let EDγ be the effective dose (ED) level at which γ% of the subjects respond. The up-and-down design typically targets the ED50 level; if other ED levels are of interest, the design may be revised to accommodate. Durham and Flournoy (1994) proposed a biased-coin up-and-down design that targets other levels such as ED25 and ED75. The up-and-down and related designs have many desirable properties. They are practically free of model assumptions and easy to implement. For a general discussion of the biased-coin up-and-down design, see Durham et al. (1997). Data analysis methods for the up-and-down design to estimate any ED levels were developed by Robbins and Monro (1951), Wetherill (1963) and Wu (1985) among others. A general review of nonparametric designs and their decision rules can be found in Ivanova (2006).

Despite its long history, design theory for binary experiments remains an active research area. For recent developments, see Li and Wiens (2011), Wang et al. (2013), Wang et al. (2015) and Wu and Tian (2013). Wang et al. (2015) considered a two-stage sequential D-optimal design. They proposed first obtaining a tentative estimate of the model parameters. The D-optimality criterion is then used to select the dose level of every additional subject. Wu and Tian (2013) presented a three-phase sequential design focusing on sensitivity. The first phase aims to ensure a viable fitted model, and the second phase chooses the dose levels to satisfy D-optimality. The third phase clusters the levels around the target ED level.

While many designs are optimal if estimating the median is the sole goal of the experiment, they are not the best when a range of ED levels are targeted. In many applications, it is desirable to accurately determine several ED levels. For example, in Rosenberger and Grill (1997), ED50 is the primary target, while ED25 and ED75 or other ED levels are also of interest. They proposed a sequential design procedure for this purpose and applied this design to a psychophysical experiment where the objective is to study how patients respond to a range of stimulus levels.

In this paper, we take a new approach in designing a binary experiment. We consider a situation where the dose–response relationship over a range of ED levels is of interest. We believe such a relationship can be well characterized after several tactically chosen ED levels are accurately estimated. Based on these considerations, we propose a two-stage sequential design. In the first stage, we employ prior information to determine a fixed-point design for a tentative estimation of the model parameters. A new method is developed to ensure sensible parameter estimation. In the second stage, we update the parameter estimation after each additional trial and select the next dose level to most efficiently estimate the target ED levels. This procedure continues until there are no more experimental subjects, or the estimates have reached a pre-specified precision. Because our design is sequential and aims to efficiently estimate several chosen ED levels, we call it two-stage sequential ED-design or simply ED-design.

The new design has been examined via simulation studies. The ED-design is indeed more efficient for estimating the targeted ED levels based on the average total root mean square error (RMSE) or the individual RMSEs. In addition, the new design is superior when tuned to target lower ED levels such as ED10 and ED25. The D-optimal design and its sequential version do not have this flexibility, and the up-and-down design cannot target more than one ED level. These results provide strong support for the proposed design.

The true dose–response relations never fully conform to the model in the real world, optimal designs do not perform at their peak levels in general. A simulation study is used to evaluate the effect of model misspecification. The new design still has the best performance in terms of the RMSE. Thus, the new design is more robust with respect to model misspecification. Finally, we provide some simulation evidence for the limiting ED-design when the sample size n goes to infinity. It appears that as a distribution over the dose range, the design has a limit with two support points. An interesting question is whether or not this is indeed the case.

We organize this paper as follows. In Section 2, we review existing results and introduce our design. Some details of the new design under a logistic regression model are given in Section 3. In Section 4, we present our simulation studies. Section 5 provides concluding remarks.

2. Review of existing designs

There is a rich literature on the design of binary dose–response experiments. We will review the designs that are most relevant to the design of this paper. The ultimate goal of such experiments is to accurately characterize the dose–response relationship. When a parametric model is specified, the experiment is often designed to maximize the efficiency of the parameter estimation. Because dose–response models are generally multiparametric, there are multiple efficiency metrics and hence many optimality criteria and design strategies.