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Implementing optimal allocation in clinical trials with multiple endpoints

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ABSTRACT

Modern clinical trials are often complex, with multiple competing objectives and multiple endpoints. Such trials should be both ethical and efficient. In this paper, we overcome the obstacles introduced by the large number of unknown parameters and the possible correlations between the multiple endpoints. We obtain the optimal allocation proportions for the following two optimization problems: (1) maximizing the power of the test of homogeneity with a fixed sample size, and (2) minimizing the expected weighted number of failures with a fixed power. Further, we implement these optimal allocations through response-adaptive randomization procedures. Our theoretical results provide the foundation for the implementation and further investigation of the procedure, and our numerical studies demonstrate its ability to achieve diverse objectives.

1. Introduction

Clinical trials are complex experiments involving human beings. They often have multiple competing objectives, such as minimizing the total number of failures and maximizing the power of detecting treatment effects. These cannot be satisfied by traditional clinical trial designs that aim to balance the patient numbers across different treatments. Response-adaptive randomization (RAR) procedures achieve these objectives by skewing the allocation probability according to the previous treatment assignments and responses. Most of the research on RAR designs has been focused on clinical trials with a single endpoint. However, in modern clinical trials multiple possibly correlated endpoints are often evaluated simultaneously, and the clinical goal is to show a positive effect for at least one endpoint. There are different rationales for multiple (composite) endpoints. First, several different endpoints may be important for the participants. Second, the investigators are not always sure which outcome indicates a treatment effect (Friedman et al., 2010). Third, embedding multiple endpoints into the analysis can help to distinguish weaker signals of treatment effects from the noises of sampling errors (Moyé, 2003). Fourth, the total event rate can be increased, which can lead to a reduction in the required sample size.

Numerous real trials currently use multiple endpoints. For example, pulmonary function, neuro-psychological status, quality of life, and mortality were all assessed in the Nocturnal Oxygen Therapy Trial (1980); the trial compared continuous oxygen (O_2) therapy and 12-h nocturnal O_2 therapy for chronic obstructive pulmonary disease. The Urokinase Pulmonary Embolism Trial (1974) explored the effect of three treatments, 12 h of urokinase, 24 h of urokinase, and 24 h of streptokinase,

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on pulmonary embolism. They considered three endpoints: angiographic severity, lung scan perfusion defects, and hemodynamic variables. Roberts et al. (1984) investigated the effect of propranolol in limiting the myocardial infarct size; their endpoints were the precordial electrocardiogram mapping, radionuclide studies, and enzyme levels. In a clinical trial of an analgesic drug used to relieve arthritic pain (Jennison and Turnbull, 1993), the primary endpoints were a measure of the pain relief experienced by the patient and the effect on the arthritic condition of the joint. Since the drug's success in relieving pain may lead the patient to be less careful of the joint, the two outcome measures might be related. These examples motivate our investigation of the use of RAR designs to find optimal allocations for clinical trials with multiple endpoints; the goal is to achieve ethical and efficient objectives.

The idea underlying RAR designs can be traced back to Thompson (1933) and Robbins (1952). The play-the-winner rule (Zelen, 1969) and the randomized play-the-winner rule (Wei and Durham, 1978) can reduce the number of patients receiving inferior treatments. Rosenberger et al. (2001) proposed an optimal allocation that minimizes the total number of failures while fixing the power. Ivanova and Rosenberger (2000) showed that an unequal allocation can sometimes result in a gain in the power. Ivanova (2003) proposed the drop-the-loser rule that achieves minimal variability. Hu and Rosenberger (2003) proved that RAR designs can increase statistical efficiency in certain clinical trials. A comprehensive introduction to RAR designs can be found in Hu and Rosenberger (2006).

Hu and Rosenberger (2003) formalized a three-step approach for the development of optimal RAR procedures. The first step is to mathematically formulate the objectives, such as maximizing the power, and to derive an optimal allocation given these objectives. For example, when comparing two binary responses with success rates p_A and p_B, given the objective of maximizing the power, the optimal allocation proportions η_A and η_B for the two treatments will be the Neyman allocation:

$$\eta_A = \frac{\sqrt{p_A(1-p_A)}}{\sqrt{p_A(1-p_A)}+\sqrt{p_B(1-p_B)}} \quad \text{and} \quad \eta_B = \frac{\sqrt{p_B(1-p_B)}}{\sqrt{p_A(1-p_A)}+\sqrt{p_B(1-p_B)}}.$$

The second step is to develop RAR procedures such as the doubly adaptive biased coin design (DBCD) proposed by Hu and Zhang (2004) to target the theoretically optimal allocation derived in the first step. The third step is to study the operating characteristics of the proposed procedure. It is clear that the derivation of the optimal allocation for certain goals is essential for RAR procedures. In addition, the closed form of the theoretically optimal allocation plays a crucial role in evaluating the properties of the RAR procedure such as the lower bound of the variability (Hu et al., 2006), although the numerical results are sufficient to apply the procedure in practice.

A general framework for the optimization problem was given by Jennison and Turnbull (1999), triggering a series of publications on optimal RAR designs with binary outcomes (Rosenberger et al., 2001; Ivanova and Rosenberger, 2001; Rosenberger and Hu, 2004; Jeon and Hu, 2012), normal outcomes (Biswas and Mandal, 2004; Zhang and Rosenberger, 2006; Gwise et al., 2008; Biswas and Bhattacharya, 2009, 2010), and survival outcomes (Zhang and Rosenberger, 2007). Tymofyeyev et al. (2007) established a general mathematical framework for obtaining optimal allocations using the Karush–Kuhn–Tucker (KKT) conditions (Kuhn and Tucker, 1951; Karush, 1939). However, all these studies explored trials with a single endpoint.

We investigate optimal allocation for clinical trials with two possibly correlated endpoints, and we implement this using RAR designs. We study how to maximize the power of a test of homogeneity for a fixed sample size and how to minimize the expected weighted number of failures (EWNF) for a fixed power. We first obtain the analytical solution of the optimal allocations for these problems. It is not trivial to check the applicability of the KKT conditions in the presence of multiple endpoints with a covariance structure. This leads to several higher-degree equations that are difficult to solve analytically. The numerical solutions are often sufficient to implement the RAR procedure. However, without the derived closed form, it is difficult to study further theoretical properties of the RAR designs, the third step of the process (Hu and Rosenberger, 2003). This is one of the major contributions of this paper. Further, we have performed comprehensive numerical studies based on simulated data and the redesign of a clinical trial. Our method is shown to be more ethical and efficient than traditional designs. The power is moderately increased and the expected number of failures among trial participants is reduced using the RAR designs for the optimal allocations. Therefore, both our theoretical and numerical results provide important insight for implementing and further investigating RAR designs in clinical trials with multiple endpoints.

This article is organized as follows. In Section 2, we present the framework, define the two optimization problems, and derive the optimal allocation proportions. In Section 3, we implement the optimal allocation using the DBCD proposed by Hu and Zhang (2004) and report the results of our numerical studies. We give a discussion in Section 4, and the proof of theorems is in the Appendix.

2. Optimization problems in clinical trials with two endpoints

2.1. Framework, notation, and optimization problems

Consider a randomized clinical trial with two treatment groups and two possibly correlated binary endpoints. Assume that there are n_A patients in treatment A and n_B patients in treatment B at the end of the trial, and let $\mathbf{n} = (n_A, n_B)$. Let (p_{A1}, p_{A2}) and (p_{B1}, p_{B2}) be the success rates of the two endpoints in treatments A and B, respectively, and ρ_A and ρ_B be the correlations between these two endpoints for treatments A and B, respectively.