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Variance-penalized response-adaptive randomization with mismeasurement

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ABSTRACT

We consider response-adaptive design of clinical trials under a variance-penalized criterion in the presence of mismeasurement. An explicit expression for the variance-penalized criterion with misclassified dichotomous responses is derived for response-adaptive designs and some properties are discussed. A new target proportion of treatment allocation is proposed under the criterion and related simulation results are presented.

1. Introduction

Randomization is an established key element for obtaining scientifically valid comparison of competing treatments in clinical trials. Ethics of randomization in clinical trials is a complex issue, and the use of response-adaptive randomizations in theoretical and practical perspectives has been explored and investigated in recent years.

A response-adaptive randomization deliberately skews the allocation probabilities of treatments based on accruing treatment allocations and responses, so that more patients are assigned to the potentially better treatment (see, for example, Hu and Rosenberger, 2006). The goal of response-adaptive procedures is to treat effectively as many patients in the trial as possible without undermining the integrity and validity of the clinical research. As a result, this scheme potentially provides a better balance between collective and individual ethics, and is morally justifiable in desperate medical situations (Pullman and Wang, 2001), and has become popular in clinical research because of its advantages in ethics, flexibility and efficiency.

As Hu et al. (2009) pointed out, the three main components of response-adaptive randomization are allocation proportion, efficiency (power), and variability. The issues of efficiency or power were developed and discussed among researchers. Hu and Rosenberger (2003) theoretically examined the relationship between the asymptotic power of the Wald test and the variance of allocation proportions, and showed that the efficiency is a decreasing function of the variability induced by the randomization procedure for any given allocation proportion. Hu et al. (2006) established a lower bound on the asymptotic variance of the allocation proportions and defined an asymptotically best response-adaptive

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randomization procedure. Hu et al. (2009) proposed a new family of response-adaptive randomization procedures that attain the lower bounds on the allocation variances for any allocation proportions, and derived the efficient procedures for several commonly used optimal allocation proportions.

In response-adaptive designs, it is expected to assign more patients to the better treatment with minimal loss of the statistical power. Yi and Wang (2009) proposed and investigated a response-adaptive design of clinical trials with a variance-penalized criterion that evaluated the performance of a response-adaptive design based on both the number of patients assigned to the better treatment and the power of the statistical test. Several authors have also examined response-adaptive randomization procedure that considered both efficiency and total number of patients receiving superior treatment (for example, Rosenberger et al., 2001; Hu and Rosenberger, 2003; Hu and Zhang, 2004; Bandyopadhyay and Bhattacharya, 2006; Cheng and Berry, 2007). However, these authors focused on perfectly measured patients responses and covariates, and did not address the important issues of misclassification probabilities for responses or covariates. In practice, it is not uncommon that the clinical trials involve covariates and/or responses that cannot be measured directly or precisely. Ignoring these imperfectly measured variables affects the quality of designs and inference of clinical trails.

Not much attention has been paid upon incorporating the problem of "errors-in-variables" (see Fuller, 1987; Carroll et al., 2006, for example) in adaptive clinical trails. It appears challenging and promising in the sense that the adaptation of the treatment allocation creates a complex dependent data structure and raises concerns about the validity of statistical conclusion, power loss of statistical tests and experimental bias with various measurement errors. Li and Wang (in press) considered a response-adaptive designs when the binary response may be misclassified, derived the optimal allocations under various objectives, and investigated asymptotically best response-adaptive randomization procedures and effects of misclassification on the optimal allocations.

Although the focus of this article is on dichotomous response, in principle, the idea may be extended to other types of responses, such as survival, continuous, longitudinal or ordinal data. For example, for continuous responses it may be possible to incorporate the Berkson's or other models of mismeasurement in the framework of this paper, although in practice computations and simulations will inevitably be tedious. As for the survival data, mismeasurement may be applied to the Cox regression and be incorporated into the framework. Extension to ordinal and longitudinal data could be slightly simpler than continuous and survival data. However, details need to be worked out to see the development. These will be our next step of research along this direction.

In this article we consider response-adaptive design with a variance-penalized criterion and discuss their optimality properties when the responses are subject to possible misclassification. The variance-penalized mean bridges the misclassification probabilities with the performance of a design according to both the mean and variability of the expected total responses. In Section 2 we review response-adaptive designs with misclassified binary responses in a multi-armed clinical trial. The variance-penalized criterion for response-adaptive randomization procedures in the presence of misclassification is described in Section 3. The optimal target function and some properties are discussed in Sections 4 and 5. Section 6 introduces a new randomization procedure for response-adaptive designs and Section 7 concludes the paper. All details of derivation are given in Appendix.

2. Response-adaptive randomization with mismeasurement

Consider a clinical trial with K treatments. There are n patients to be treated in the trial, each of whom is to randomly receive one and only one treatment. Each patient's response after treatment is immediate and dichotomous (with 1 representing success and 0 representing failure). A response-adaptive design consists of a randomization matrix $\boldsymbol{T}=(\boldsymbol{T}_1,\ldots,\boldsymbol{T}_n)$ of size $k\times n$, where $\boldsymbol{T}_i=\boldsymbol{e}_k$, $k=1,2,\ldots,K$, and $\boldsymbol{e}_k$ is a $K\times 1$ vector with a 1 in the kth entry and zero elsewhere, for each $i=1,2,\ldots,n$. Clearly, $T_{ki}=1$ means that the ith patient receives treatment k.

Let $\tilde{\boldsymbol{Y}}_i=(\tilde{Y}_{1i},\ldots,\tilde{Y}_{Ki})'$ and $\boldsymbol{Y}_i=(Y_{1i},\ldots,Y_{Ki})'$ be the vectors of response variables, where Y_{ki} and $\tilde{Y}_{ki}$ are respectively the true and misclassified responses of the ith patient who receives treatment k, $i=1,2,\ldots,n$, $k=1,2,\ldots,K$. The variable $\tilde{\boldsymbol{Y}}_{i+1}$ is assumed to be independent of $\tilde{\boldsymbol{Y}}_1,\ldots,\tilde{\boldsymbol{Y}}_i,\boldsymbol{T}_1,\ldots,\boldsymbol{T}_i$. However, $\boldsymbol{T}_i$ depends on $\tilde{\boldsymbol{Y}}_1,\ldots,\tilde{\boldsymbol{Y}}_{i-1},\boldsymbol{T}_1,\ldots,\boldsymbol{T}_{i-1}$. Note that only one entry of $\tilde{\boldsymbol{Y}}_i$ is observable and $\boldsymbol{Y}_i$ is unobservable.

Define the misclassification probability vectors $\boldsymbol{\gamma}=(\gamma_1,\ldots,\gamma_K)'$ and $\boldsymbol{\delta}=(\delta_1,\ldots,\delta_K)'$, where

$$\gamma_k=\mathrm{P}(\tilde{Y}_{ki}=1\,|\,Y_{ki}=0)\quad\text{and}\quad\delta_k=\mathrm{P}(\tilde{Y}_{ki}=0\,|\,Y_{ki}=1),$$

$i=1,\ldots,n$, and $k=1,\ldots,K$. In epidemiology, γ_k is the probability that a true negative ($Y=0$) on treatment k is misclassified as a positive ($\tilde{Y}=1$), while δ_k is the probability that a true positive is misclassified as a negative. Commonly $1-\gamma_k$ and $1-\delta_k$ are referred to "Specificity" and "Sensitivity", respectively. Their magnitudes reflect the severity of the misclassifications.

Note that the misclassification probabilities $\boldsymbol{\gamma}$ and $\boldsymbol{\delta}$ are assumed to be pre-fixed and non-random, and need not be estimated adaptively in our study. In reality, sensitivity and specificity can be estimated sequentially and applied to the randomization procedure, as the sequential estimation of the target proportion being applied to the doubly adaptive biased coin design (DBCD, Hu and Rosenberger, 2003; Hu and Zhang, 2004). Intuitively, the estimated misclassification probabilities would gradually vanish to zeroes as information for classifying the responses accumulates.

Assume further that $\boldsymbol{Y}_1,\ldots\boldsymbol{Y}_n$ are independent and identically distributed such that Y_{ki} follows the Bernoulli(p_k) distribution, where $p_k=\mathrm{P}(Y_{ki}=1)$ is the probability of success for the kth treatment. For $k=1,\ldots,K$ and $i=1,\ldots,n$, the