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Design of experiments for a confirmatory trial of precision medicine

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ABSTRACT

Precision medicine, aka stratified/personalized medicine, is becoming more pronounced in the medical field due to advancement in computational ability to learn about patient genomic backgrounds. A biomaker, i.e. a type of biological process indicator, is often used in precision medicine to classify patient population into several subgroups. The aim of precision medicine is to tailor treatment regimes for different patient subgroups who suffer from the same disease. A multi-arm design could be conducted to explore the effect of treatment regimes on different biomarker subgroups. However, if treatments work only on certain subgroups, which is often the case, enrolling all patient subgroups in a confirmatory trial would increase the burden of a study. Having observed a phase II trial, we propose a design framework for finding an optimal design that could be implemented in a phase III study or a confirmatory trial. We consider two elements in our approach: Bayesian data analysis of observed data, and design of experiments. The first tool selects subgroups and treatments to be enrolled in the future trial whereas the second tool provides an optimal treatment randomization scheme for each selected/enrolled subgroups. Considering two independent treatments and two independent biomarkers, we illustrate our approach using simulation studies. We demonstrate efficiency gain, i.e. high probability of recommending truly effective treatments in the right subgroup, of the optimal design found by our framework over a randomized controlled trial and a biomarker–treatment linked trial.

1. Introduction

A randomized controlled trial (RCT) has been the gold standard for testing a new intervention in medicine, especially in phase III confirmatory studies. Many treatments work differently in different patient subgroups, and in this case RCTs which enroll all patients are not necessarily the most efficient approach in phase III. Instead enriched designs that recruit patients likely to benefit have considerable advantages. There is a danger that enriching a phase III trial too much may lead to missing out on a patient subgroup that would have actually benefited.

This therefore motivates phase II trials of targeted agents investigating not only whether a drug works but in which patient subgroups it works in. Several 'biomarker-driven' trial designs have been proposed to allow investigation of multiple treatment arms in different patient subgroups (Buxton et al., 2014; Kaplan et al., 2013; Kaplan, 2015; Middleton et al., 2015). In the case where each treatment can be tested in each subgroup, the number of hypotheses to be tested in a trial can be very large. Some recent papers providing an overview of biomarker-driven trial designs include Antoniou et al. (2016), Renfro and Sargent (2017), Antoniou et al. (2017) and Parmar et al. (2017).

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One important aspect of biomarker-driven trial designs that has not been well researched is how to use the information collected from a phase II trial assessing multiple treatments and biomarkers to design the most efficient phase III designs. In particular it would be very useful to have a framework which determines which treatments should be tested in phase III, and in which biomarker subgroups. There has been some work in the context of evaluating a single experimental treatment (Ondra et al., 2016), but to our knowledge none that investigates novel multi-arm phase II biomarker-driven trial designs.

Considering a regression model with first order interaction terms, we propose a tool to design a confirmatory trial based on the analysis of an observed phase II trial or a historical study. There are two elements in this tool: Bayesian data analysis on data of a phase II trial, and the application of design of experiments to finding an optimal design for future experiment. The focus of our tool is to find an efficient design that could reject false null hypotheses in the confirmatory trial with high power.

Bayesian data analysis is a flexible approach where the knowledge and confidence of clinicians can be incorporated into the framework via the specification of a prior distribution. When the sample size of the observed trial is small, we suggest bootstrapping the data for the Bayesian analysis, and conjecture a subset of hypotheses that would be tested in a confirmatory trial based on a posterior predictive distribution from the analysis. We then use the notion of design of experiments to find the optimal treatment randomization scheme for the future experiments based on these information. Design of experiments is an approach that provides guidance on data collection such that sufficient information could be collected for a future experiment. We consider a weighted version of L-optimal criterion that resemble the idea of Morgan and Wang (2010) where they consider weighted D-, A-, and E-optimal designs for a factorial model. Sverdlov and Rosenberger (2013) review methods on finding optimal allocation for multi-arm clinical trials, where the design depends on the unknown parameters of a factorial model. We note that the Bayesian data analysis in our framework is independent of the commonly used Bayesian optimal design framework, see for example Kathryn and Verdinelli (1995) for the review on Bayesian optimal design framework. Our framework can be generalized to finding a Bayesian optimal design for generalized linear and nonlinear models.

The structure of the paper is as follows. We present a statistical model and hypothesis testing procedure for the trial with biomarker setting in Section 2. We introduce our novel design approach in Section 3, and conduct simulation study to compare the performance of the proposed optimal designs with two commonly employed designs in Section 4. We discuss our work and provide some insights into future research topics in Section 5.

1.1. Motivating trial

As the motivation for the work that follows, we consider a phase II trial that, at the time of writing, is under consideration for funding. This trial will test two experimental targeted treatments (T1 and T2), against chemotherapy control, for high grade serous ovarian cancer. Two biomarkers are included (B1 and B2) with it being thought likely (but not definite) that T1 will work best in B1 positive patients and T2 in B2 positive patients. Patients can be positive for B1, B2, both or neither.

The endpoint used for efficacy is six month change in the level of circulating tumor DNA in the blood, which will be treated as normally distributed on the log scale. The objective of the phase II trial is to determine which of T1 and T2 should be tested in a larger phase III trial, and in which patient subgroups. The methodology in this paper will be used for helping to make this decision.

2. Background and notation

Let vector $x_i = (x_{i1}, \ldots, x_{iL})$ be a biomarker profile of patient i where $x_{il} = 1$ represents patient i is positive for biomarker l, and $x_{il} = 0$ otherwise, $l = 1, \ldots, L$; T_{ik} be the experimental treatment indicator where $T_{ik} = 1$ indicates that patient i receives treatment k. The response model for patient i is

$$y_i = \alpha + \sum_{k=1}^{K} T_{ik}\beta_k + \sum_{l=1}^{L} x_{il}\gamma_l + \sum_{k=1}^{K}\sum_{l=1}^{L} T_{ik}x_{il}\delta_{kl} + \epsilon_i,$$

where α is the placebo/control effect for a patient with a negative biomarker profile, i.e. $x_i = (0, \ldots, 0)$, β_k is the main effect of experimental treatment k, γ_l is the main effect of biomarker l, and δ_{kl} is the interaction between treatment k and biomarker l. A placebo/control treatment is indicated by $T_{ik} = 0, \forall k = 1, \ldots, K$. The residual errors, ϵ_i, are assumed to be identically and independently distributed, and that they are normally distributed with zero mean and a common variance σ^2, i.e. $\epsilon_i \overset{iid}{\sim} N(0, \sigma^2), i = 1, \ldots, n$.

As an example, consider a trial where there are two experimental treatments and two biomarkers, i.e. $K = 2$ and $L = 2$, and that each patient receives only one treatment (either $T_{i1} = 1$ or $T_{i2} = 1$) or a placebo/control treatment, $T_{i1} = 0$ and $T_{i2} = 0$. The response model is

$$\begin{aligned} y_i &= \alpha + \beta_1 T_{i1} + \beta_2 T_{i2} + \gamma_1 x_{i1} + \gamma_2 x_{i2} + \delta_{11} x_{i1} T_{i1} + \delta_{12} x_{i2} T_{i1} + \delta_{21} x_{i1} T_{i2} + \delta_{22} x_{i2} T_{i2} + \epsilon_i \\ &= f(x_{il}, T_{ik})\theta + \epsilon_i, \end{aligned} \tag{1}$$

where

$$f(x_{il}, T_{ik}) = (1,\ T_{i1},\ T_{i2},\ x_{i1},\ x_{i2},\ x_{i1}T_{i1},\ x_{i2}T_{i1},\ x_{i1}T_{i2},\ x_{i2}T_{i2})$$

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