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Statistical issues in trial design and personalized medicine

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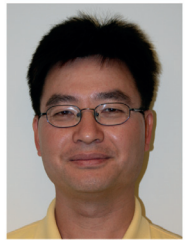

"New and general statistical methods are needed to analyze clinical data for personalized medicine. Specifically, it is important to address the following questions: are the most classical statistical methods ... still valid? Can one use some nonparametric methods, such as rerandomization tests? How does one perform subgroup statistical analysis?"

Personalized medicine is an approach that will allow physicians to tailor a treatment regimen based on an individual patient's characteristics (which could be biomarkers or other covariates). Over the past several decades, fields of translational research (genomics, proteomics and metabolomics) have enabled the study of genes, proteins and metabolic pathways to human physiology and variations of these pathways that may lead to disease susceptibility. One can apply pharmacogenetics to our understanding of which patients should or should not receive a drug based on their personal information.

Scientists have identified many new biomarkers that may be linked with certain diseases. Clinical trials are the next important step to develop personalized medicine in order to confirm the findings from different research studies. As stated by M Hamburg (commissioner US FDA, MD, USA), "new designs for clinical trials are needed so that genetics or other markers can be used to assist in patient selection [1]." To design a superior and more efficient clinical study for personalized medicine, one should incorporate information of important biomarkers. These biomarkers are usually called covariates in statistical literature [2].

In clinical trial designs that incorporate a patient's covariate information, there are two types of designs according to the classification of Hu and Rosenberger [2]: covariate-adaptive designs and covariate-adjusted response-adaptive (CARA) designs. In the literature, covariate-adaptive designs are proposed to balance treatment assignment with respect to key covariates of interest [3,4], whereas CARA designs were developed only recently [5,6].

In this article, we discuss issues of design and statistical inference related to clinical trials for personalized medicine. We describe clinical trials for personalized medicine in three aspects:

- New designs of clinical trials and their properties;
- Corresponding statistical inference and interim analysis (sequentially monitoring);
- Missing data and other practical problems in clinical trials.

Each of the above three aspects is crucial for the success of a clinical trial for personalized medicine.

New designs that incorporate important covariate information

Personalized medicine raises new challenges for the design of clinical trials, such as:

- More covariates (biomarkers) have to be considered;
- Particular attention needs to be paid to the interaction between treatment and covariates (biomarkers).

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To design a good clinical trial for personalized medicine, we need new designs that can match the special features of personalized medicine.

First, for clinical trials involving important covariates (biomarkers), the first concern of a clinician is the balancing of these covariates for a simple treatment comparison. Second, we consider optimal designs that achieve efficiency in detecting treatment differences and interaction effect. Most existing literature leaves the optimal designs for detecting interaction effect unexplored. Ethics has always been a great concern in the design of clinical trials. A challenge raised by personalized medicine is how to incorporate covariate information in response-adaptive randomization, while considering issues of both efficiency and medical ethics. It is important to develop a unified family of CARA randomization based on both optimization and ethics.

■ New designs for balancing important covariates (biomarkers)

Taves summarized most of the published clinical trials (over 50,000 trials) conducted from 1989 to 2008 [7]. Stratified permuted block (SPB) design was used to balance covariates in most trials [2]. Covariate-adaptive designs (based on minimization) have been increasingly used in clinical trials [3,4]. There are approximately 500 trials that used covariate-adaptive designs to balance covariates from 1999 to 2008. Three types of imbalances are usually considered in literature: within-strata imbalance, marginal imbalance and overall imbalance.

The SPB design has the following two important drawbacks:

- Permuted block design is subject to selection bias at the end of each block, when one treatment group has already had one half of the patients [8];
- With a moderate sample size and a large number of covariates (most strata have very few patients), the SPB design is almost equivalent to complete randomization, whose marginal imbalance and overall imbalance can be extremely large [9].

Therefore, the SPB may not be a suitable design for some clinical trials of personalized medicine.

Minimization methods (covariate-adaptive designs) are an alternative to the SPB [3,4]. Simulation studies found that these methods indeed reduce marginal imbalances, as well as the overall imbalance [10]. However, Pocock and Simon's method tends to have large imbalances within individual strata [10,11]. Moreover, Pocock and Simon's method is only studied by simulations. There is "no theoretical justification that the procedure even works as intended" [6].

It is crucial and urgent to develop efficient randomization procedures that achieve balance at all three levels: within-stratum, within-covariate margins and overall. Motivated by the above objective, a new family of randomization procedures was recently proposed by considering the weighted average of all three types of imbalance [12]. The proposed procedure distinguishes itself from stratified randomization and Pocock and Simon's method by dealing with all three types of imbalance simultaneously, rather than focusing on one in particular. However, this is just a start as more innovative designs are needed in this area.

■ Optimal design for detecting important interactions among treatments & biomarkers

The goal of a conventional clinical trial is to determine if a new treatment is superior. When designing a clinical trial for personalized medicine, the goal is not limited to just detecting the treatment difference, but also to identifying biomarkers that predict the efficacy of treatments. Therefore, the interaction between the treatment and the biomarker becomes especially important. As a result, it is important to have a design that can detect the interaction between treatment and biomarkers efficiently. For a clinical trial involving several covariates, classical types of optimal design may not be suitable due to the complexity of the covariate matrix. New and innovative designs are needed in this area.

■ Optimal designs based on both efficiency & ethics

Clinical trials require stringent ethical considerations, because they involve human subjects. One ultimate objective is to develop new families of designs that can efficiently use all the available information and also preserve medical ethics. Ethics may require us to minimize the number of subjects treated in the inferior treatment. Efficiency refers to maximizing the power of relevant test; however, efficiency and ethics often conflict with each other. A balance between optimization and ethics is needed. To develop personalized medicine, covariate information plays an important role in the design and analysis of clinical trials. A challenge is the incorporation of covariate information in design, while still considering issues of both efficiency and medical ethics. To address this problem, new designs of clinical trials are needed.

Statistical inference

More biomarkers (covariates) are used in the selection of treatments, which means that covariate-adaptive designs or CARA designs should be implemented in clinical studies:

- Complex data structure: dependence (the data generated from the corresponding clinical trials are sequentially dependent), more covariates (large number of strata and relatively small number of patients in each stratum).

- Subgroup statistical analysis: in personalized medicine, one may be interested in certain types of biomarker, and only needs to consider data from these subgroups;

New and general statistical methods are needed to analyze clinical data for personalized medicine. Specifically, it is important to address the following questions: are the most classical statistical methods (such as statistical methods based on maximum likelihood estimators or moment estimators) still valid? Can one use some nonparametric methods, such as rerandomization tests? How does one perform subgroup statistical analysis?

Rosenberger and Sverdlov gave an overview of covariate-adaptive randomization methods [6]. Recently, Shao *et al.* established a general theory for testing hypotheses for clinical trials using covariate-adaptive randomization [13]. For CARA randomization procedures, some preliminary results can be found in Zhang *et al.* [5]. However, their results do not apply to general clinical studies for personalized medicine. General statistical methods for personalized medicine are needed.

An alternative to using traditional large-sample population-based tests to analyze clinical trials data is to use randomization as a basis for inference by computing rerandomization tests [14]. Randomization tests have not been well-studied for clinical trials based on adaptive randomization and this is a topic for future research. There is no general method about how to perform subgroup statistical analysis for personalized medicine.

Sequential monitoring and interim analysis have become standard techniques in conducting clinical trials. The main advantages of sequential monitoring are listed in Jennison and Turnbull [15]. First, it is ethical to monitor clinical trials sequentially, because one can ensure that patients are not exposed to dangerous treatments and can stop trials as soon as possible if needed. Second, administratively, one needs to ensure that the protocol is not violated, and that the assumptions on which the clinical trial is based are correct and valid. Third, sequential monitoring can reduce sample size and cost. Zhu and Hu studied sequentially monitoring a clinical trial based on response-adaptive designs [16]. Since personalized medicine usually involves covariate information, it is unclear how to perform sequential monitoring and interim analysis of a clinical trial for personalized medicine.

Practical issues

To conduct clinical trials for personalized medicine, one often faces the following issues in practice:

- Missing data;
- Population heterogeneity;
- Delayed responses.

Many popular statistical techniques to handle missing data have been proposed and studied in statistical literature [17].

Missing data are often encountered in clinical studies. Molenberghs and Kenward have an extensive discussion regarding the application of various missing data methodology in clinical trials [18]. However, their attention has primarily focused on fixed designs. For randomized clinical trials for personalized medicine, investigating the impact of missing data and developing suitable missing data approaches are indispensable. To deal with population heterogeneity and delayed responses in clinical trials, some theoretical studies are available in the literature [2,19,20]. It is important to study the effects of both population heterogeneity and delayed responses of clinical trials for personalized medicine.

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