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The pursuit of balance: An overview of covariate-adaptive randomization techniques in clinical trials

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ABSTRACT

Randomization is fundamental to the design and conduct of clinical trials. Simple randomization ensures independence among subject treatment assignments and prevents potential selection biases, yet it does not guarantee balance in covariate distributions across treatment groups. Ensuring balance in important prognostic covariates across treatment groups is desirable for many reasons. A broad class of randomization methods for achieving balance are reviewed in this paper; these include block randomization, stratified randomization, minimization, and dynamic hierarchical randomization. Practical considerations arising from experience with using the techniques are described. A review of randomization methods used in practice in recent randomized clinical trials is also provided.

1. Introduction

Over the seventy years since the first randomized, controlled trial (RCT) in clinical medicine, RCTs have become firmly established as the gold standard of clinical research [1]. Randomization, in conjunction with blinding where possible, provides a fundamental tool for eliminating bias in treatment assignment and achieving precise and valid estimates of the treatment effect. The International Conference on Harmonization (ICH) guideline on statistical principles for clinical trials summarizes the key benefits of randomization as follows [2]:

> *Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.*

Although the method of randomization can be as simple as flipping a coin, such simple randomization may result in imbalanced sample size and baseline characteristics (i.e. covariates) among various treatment groups [3,4]. These chance imbalances in group size and baseline covariates, which have long been realized and discussed, can influence the comparison between treatment groups and introduce potential bias or confounding. Various techniques have been developed to address these issues, including block randomization, stratified randomization, and covariate-adaptive techniques, which have become more and more frequently adopted by today's clinical trialists. Each technique has its advantages and disadvantages, which must be carefully considered before a method is selected.

The objective of this review is to assess the state of the art in randomization techniques and evaluate the utilization of these techniques in RCTs. A brief overview of simple randomization and block (unstratified) randomization is provided; but the focus of this review is on randomization methods for achieving the balance of important baseline covariates. The pros and cons of each method are evaluated and practical considerations arising from experience with using these methods are discussed. Finally, we performed a review of randomization methods used in practice in recent randomized clinical trials.

2. Conventional randomization methods

In this section we describe the "conventional" randomization methods – methods that do not control for the balance of covariates – and why these methods may be limited in the design of clinical trials.

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2.1. Simple randomization

Randomization based on a single sequence of random assignments is known as simple randomization [5]. Also known as "complete" randomization, it prevents any conscious or unconscious selection bias by allocating subjects to treatment groups completely at random. The most common and basic method of simple randomization is flipping a fair coin.

Despite simple randomization's usefulness in mitigating selection bias and forming the basis for statistical analysis, it may lead to chance imbalances in group sizes and in the distribution of key baseline covariates, which may in turn cause "accidental" bias [6]. Clinical trials with substantial imbalances often come under criticism, even when these imbalances are due to chance alone [7,8] or to randomization methods that do not control for balance [9,10]. Imbalances in baseline subject characteristics are often blamed when trials fail to show the expected treatment effects [11]. For these reasons, more and more trialists today have being turning to methods that, in contrast to simple randomization, ensure balance (to some extent) with respect to group sizes and pre-specified baseline characteristics.

2.2. Block randomization

The method most commonly used to balance the group size (i.e. overall balance) is the unstratified permuted-block randomization (PBR) or block randomization which randomizes participants within blocks. Blocks are small and balanced with predetermined group assignments, which ensure that the treatment groups are balanced for the overall trial, both as the trial progresses and at the trial's end. Although balance in sample size may be achieved with this method, groups may be generated that are incomparable in terms of certain covariates.

3. Randomization methods for achieving covariate balance

Ensuring balance in important prognostic covariates across treatment groups is desirable for a number of reasons. When interim analyses are planned, ensuring covariate balance throughout the trial increases precision at the time of the interim where the number of subjects is small. Similarly, it increases the precision of subgroup analyses or tests for interaction between treatment and potential prognostic factors. It also decreases excess noise in clinical trial data to allow for maximal power of detecting the treatment effect in primary and secondary outcome analyses. Last but not least, with the advancement of modern technologies such as Interactive voice response (IVR) and interactive Web response (IWR) systems, the organizational effort and costs involved in ensuring balance in randomization have become relatively small. Hence the pursuit of balance can be viewed as a low-cost insurance policy against the likelihood of extreme imbalances, albeit the chance of such imbalances occurring might be low.

The techniques for achieving covariate balance (i.e. covariate-adaptive randomization methods) can be generally divided into three categories: (1) stratified (block) randomization, (2) minimization, and (3) dynamic hierarchical randomization. We review and evaluate each technique in detail in this section.

3.1. Stratified (block) randomization

The most common way to achieve balance in given baseline covariates (i.e. factors) is stratified randomization. It creates a separate randomization schedule, most commonly a permuted block schedule, for each unique stratification cell (i.e. stratum) formed by the combination of the levels of covariates [2,4]. Some commonly controlled stratification factors include center, disease stage, baseline medication, etc. In our experience, the stratified permuted block randomization (stratified PBR) is the most used randomization method in both academic and industry sponsored clinical trials.

3.1.1. Choice of block size and predictability

Care should be taken to choose block sizes for stratified PBR. They should be sufficiently short to limit possible imbalance, but long enough to avoid predictability towards the end of the sequence in a block. Having many stratification factors may lead to many incomplete blocks and thereby imbalance. Therefore choice of block size(s) should as well take into account the number of stratification factors [4]. A variant of stratified PBR that uses varied block sizes (e.g. a mixture of blocks of size 2, 4 or 6 at random) may be employed with the intention of making it harder for the investigator to guess the next treatment assignment and hence reducing the potential selection bias [2].

A common criticism of stratified PBR, and block randomization as a whole, is that it is overly restricted and provides substantial potential for selection bias as the treatment allocation is predictable towards the end of a block [12]. Berger suggested that block randomization should not be used at all for this reason [13]. To overcome the deterministic features of block randomization, Berger et al. proposed the maximal procedure [14], which generates the least restrictive allocation procedure subject to a constraint on the maximum tolerated imbalance. Soares and Wu proposed the big stick design, which has high allocation randomness but is limited to two-treatment balanced allocation scenarios only [15]. Zhao and Weng proposed the blocked urn design that is applicable to trials with more treatments and balanced or unbalanced allocations [16].

3.1.2. Limitations

The popularity of the stratified PBR among clinical trialists is greatly attributed to its ability to achieve balance within strata and its ease of use. However, as pointed out by several authors [12,17], with the stratified PBR severe imbalance can still occur for the overall treatment assignments, especially if there is a large number of incomplete blocks at the end of the trial. It may also results in imbalance at the individual prognostic factor level, i.e. marginal imbalance, which would affect the inference if an additive model is adopted for the analysis. To avoid severe imbalances at the trial level, Lin and Su's modified PBR is an option where the balance for the overall treatment assignment is maintained by checking the overall imbalance whenever a new block is opened during the PBR procedure [18].

A more important limitation of stratified PBR is that it can only balance a small number of factors. When there are too many strata relative to the number of subjects, some strata will have few or no subjects resulting in an inadequate balance at the individual strata level, at the covariate level, or for the study as a whole [19]. Therneau reported that the balance in covariates begins to fail when the total number of distinct combinations of factor levels approaches half the sample size [20]; while Kernan suggest that the number of strata be limited to N/4B, where N is the total sample size and B is the block size, with 4 being a safety factor [4]. The number of covariates that can be balanced is hence largely limited in smaller studies. Similarly in multicenter trials with a large number of sites, stratification beyond site is often prohibited if stratified PBR is used.

3.2. Minimization

When there are many important prognostic factors to handle, the so-called covariate-adaptive allocation procedures can be used to provide a balance in selected covariates [2]. Minimization, first described by Taves [21] and expanded by Pocock and Simon [22], is the most commonly used covariate-adaptive randomization method. It achieves the balance in treatment assignments across factor levels by choosing the allocation for the new subject that would lead to the smallest degree of imbalance possible across the set of his/her baseline characteristics.

Specifically, suppose the trial has already entered some subjects and the next subject is to be randomized. The minimization method