Randomization in clinical trials

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I am planning a study to evaluate the effect of Remdesivir on mortality among hospitalized COVID-19 patients. There will be two arms in the study, including a group treated with Remdesivir and a control group. Because age and BMI are considered risk factors associated with mortality in these patients, it is necessary that the two groups are comparable in both age and BMI. It seems that this requirement can be achieved by appropriate randomization, and I am wondering what randomization method is best to achieve the desired requirement.

Randomized clinical trials (RCT) are considered the gold standard for evaluating the causal relationship between an intervention/treatment and a clinical outcome. By randomly assigning subjects to the study arms, an RCT is designed to balance the treatment assignments for the known and unknown baseline confounding factors that might affect the outcome among arms and eliminate other types of bias.[1,2]

The concept of randomization was first introduced by R. A. Fisher in 1925.[3] He stated that randomization is an essential ingredient in the design and analysis of experiments.

1. Reasons for randomization

1.1 To balance all known and unknown factors among treatment arms

The goal of an RCT is to establish a cause and effect relationship between treatment and outcome. Without randomization, such a relationship can be biased by confounding variables. For example, in the proposed study, if more younger patients are assigned to the Remdesivir arm, compared to the placebo arm, and because younger patients tend to have lower in-hospital mortality, thus, even if Remdesivir has no treatment advantage compared to placebo, patients who received Remdesivir will still have lower mortality due to lower age, and the result will be misleading due to confounding by age. This problem of confounding also applies to all unknown risk factors that might be associated with the outcome. By randomizing patients to the treatment arms, all unknown factors are expected to be balanced among the arms in a long run, so the potential for bias caused by imbalanced unknown risk factors can be minimized.

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1.2 To minimize predictability of treatment assignments

Very often, researchers involved in an RCT will have some expectations on the effectiveness of the treatments. Should the treatment assignments be predictable, then there will be a layer of potential selection bias that might jeopardize the validity of a study. For example, if a researcher has an expectation that the Remdesivir treatment is better than the placebo, and the researcher can accurately predict the treatment assignment for the upcoming patients, then it is possible that patients selected to receive the treatment would not represent the same population as the control group. Therefore, the results from such a study could be distorted by this bias.

Randomization has a key role in an RCT, and many randomization methods have been developed to satisfy various considerations of RCTs.[9]

2. Randomization methods

2.1 Simple randomization

Simple randomization is the most basic randomization method. It features a complete randomness in

assigning subjects to a treatment arm. The basic idea of this technique can be illustrated by tossing a fair coin. For example, if the side of the coin is heads, then a patient is assigned to the Remdesivir group; otherwise, if a tails, then to the placebo group. Because it is a fair coin, in a long run, 50% of the patients will receive Remdesivir, and 50% will receive placebo. Some statistics text books have a random number table in the appendix, and many computer programs have functions to generate randomization numbers, and very often, those numbers are reproducible.

While simple randomization is often the method of choice when the study sample size is large, it might result in substantially unbalanced treatment assignments when the study sample size is small. In the case of tossing a fair coin, if a large number of tries are made, it is likely that the numbers for heads and tails are equally 50%. However, it won't be surprising if there are 3 heads and 7 tails, if a coin is only tossed 10 times. In fact, such unbalanced assignments often translate into decreased statistical power, which renders the study less efficient. On the other hand, under certain circumstances, an unbalanced allocation ratio might be preferable. For example, the recruitment might be easier if the potential participants are told that there will be a 2:1 allocation ratio of active to placebo treatment in a study, and most of the participants prefer active treatment.

Regardless of the allocation ratio, simple randomization can result in an allocation that substantially differs from what is planned if the sample size is small. To avoid such a problem, a block randomization can be used.

2.2 Block randomization

Block randomization was developed to facilitate the randomization process to achieve a planned allocation ratio.[5] Specifically, a block is a subset of the study subjects that does not have any significance other than as a randomization unit. To start, the size of a block will be defined. It must be multiples of the number of treatments, while considering the planned allocation ratio. For example, if there are 2 treatments, and the allocation ratio is 1:2, then the block size can be 3, 6, 9, etc. Next, for a specific block size, all possible balanced assignment sequences will be calculated, using methods, such as permutations, and each block will randomly choose one of the sequences to determine treatment assignments.

There are considerations for determining a block size. In general, a smaller block size increases predictability. For example, if a block size of 3 is used in the example above, then it is easy to predict what the last treatment would be in a block, i.e., the treatment that has not been assigned according to the planned proportion will be the next treatment, which is deterministic. This might, however, result in selection bias when the study arms are unmasked. On the other hand, a larger block size might result in an undesirable allocation ratio in the middle of a study. If interim analyses are planned and treatment allocations are expected to be balanced at all the interims, then a block randomization might not work well. To address this issue, the "blocked randomization with randomly selected block sizes" was introduced. In this design, the block sizes are not fixed, but randomly chosen from several possible sizes. Because the size of each block cannot be predicted, it is difficult to predict which treatment will be the last one in a block.

While block randomization works well for ensuring a desirable treatment allocation ratio, it has no control over whether the risk factors are balanced among the arms, especially in small studies. Note that such risk factors include both known and unknown factors, and many methods have been introduced to balance the known risk factors. Furthermore, although certain analysis methods can be used to adjust for known risk factors, they might not work well if there are interactions between treatment and those factors.

2.3 Stratified randomization

Stratified randomization is one of the methods developed for balancing known risk factors. It starts with stratifying the whole study population into strata, which are subgroups with the same characteristics. For example, if age is considered as a risk factor, then the whole study population can be divided into two strata, e.g., patients <65 and ≥ 65 years old. Then within each stratum, a block randomization can be performed. As a result, if the treatments within each stratum are balanced, then the corresponding risk factor–age–will be automatically balanced across treatments.[8]

Because stratified randomization prevents imbalance of known risk factors, it improves power for small trials, if the stratified factors have a large effect on the outcome. In addition, stratified randomization also facilitates subgroup analysis and interim analysis. Note that, in data analysis of studies with stratified randomization, all stratification factors should be adjusted in the statistical models.

While stratified randomization has many desirable properties, there are also limitations. For example, stratified randomization works better if the distributions of the risk factors are well understood. Otherwise, there might be challenges to properly define the strata. For example, if a large majority of the study participants are <65 years old, then stratifying participants by 65 years old is problematic because there will not be a lot of participants in the ≥65 years old stratum, and the stratification is not efficient.

In addition, stratified randomization would not work well if a large number of risk factors need to be stratified. For example, if there are two risk factors, including age, which has two strata, and BMI, which has three strata (underweight, normal, and overweight), then the combination will have $2 \times 3 = 6$ strata. This number grows rapidly if the number of factors is large. If a large number of risk factors need to be balanced, the adaptive randomization method might be a better choice.

2.4 Adaptive randomization

There are different types of adaptive randomizations, including covariate-adaptive randomization and response-adaptive randomization, and we will focus on the former in this article.

Minimization was the first covariate-adaptive randomization method introduced. It is a dynamic method that minimizes imbalance in the distributions of treatment numbers within the levels of each individual risk factor. In general, minimization randomization starts with randomizing the first several subjects using simple randomization. Subsequent subjects are allocated by a probability calculated using the information of the subjects already randomized, so that the imbalance is minimized. There are different ways to calculate such a probability, and several different methods have been developed, including those developed by Hu and Hu,[4] and Pocock and Simon.[7] The R package *carat* can be used to calculate the assignment probabilities.

3. Some considerations

3.1 No "failed" randomization

Sometimes, the treatment/risk factors might not balance well after randomization; however, that does not mean that the randomization "failed."[6] In fact, randomization is a process, not an outcome, so that even if there are imbalances, the imbalances are part of the random process, and thus a randomization cannot "fail," if implemented correctly.

3.2 Randomness vs. deterministic

For smaller studies, methods such as block randomization, stratified and adaptive randomization are preferable, because they often achieve better balance compared to simple randomization. However, these methods are often associated with less randomness. In general, the stronger the restriction, the better the balance, and the more deterministic the process is.

In summary, randomization is an essential component of a successful RCT, and it helps prevent all sorts of biases. Many randomization methods have been developed to satisfy various study requirements. For larger studies, simple randomization might be a good choice because the randomization mechanism is simple, and, if the study size is sufficiently large, it balances the treatment assignments for all the known and unknown confounding factors. For smaller studies, other randomization methods can achieve better balance, at the expense of being more deterministic. There is no "failed" randomization if an appropriate method is chosen and implemented correctly.

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