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REVIEW ARTICLE

Application of Randomization Techniques for an Unbiased Assessment of Outcome in Clinical Studies

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ABSTRACT

In human clinical trials and biological experiments, randomization has been extensively used as a method of experimental control. It insures against the accidental bias and helps in preventing the selection bias. In treatment assignments, it eliminates the source of bias and produces the comparable groups, thereby expressing the likelihood of chance as a source for the difference of end outcome by permitting the use of probability theory. This study covers different methods of randomization and the use of online statistical computing web programming www.randomization.com for generating the randomization schedule. Issues related to randomization are also discussed in this study.

Keywords: Block, Covariate, Patient, Qucikcalc, Randomization, Stratified, Treatment.

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INTRODUCTION

The bias of an evaluation is minimized by a good experiment or trial as it avoids confounding raised from other known and unknown factors. Randomization ensures that each patient under study bears an equal chance of receiving any of the treatments and generates comparable intervention groups, which are similar in all important aspects other than for the intervention each group receives. It also paves a way for providing a basis for the statistical methods used in the data analysis. Randomization is considered to be the most reliable form of scientific evidence, which influences the health care policy and practice as it reduces vigorous anonymity and variability. In general, for testing the efficacy of the treatment, a randomized experiment is an essential tool.

In reality, randomization requires the generation of reproducible randomization schedules. Generating a randomization schedule includes acquiring the random numbers and assigning them to each subject or treatment conditions. These random numbers can be generated by computation or they can come from random number tables found in various statistical textbooks. In case of a simple experiment with small number of subjects, randomization can be easily performed by assigning the random numbers from the random number tables to the treatment conditions. Whereas, in the large sample size or if restricted randomization or stratified randomization is to be performed for an experiment or if an unbalanced allocation ratio is used, it is better to make use of computation to do the randomization, such as SAS, R programming, etc.[1-6]

NEED FOR RANDOMIZATION

Life science researchers demand randomization for various reasons. First, there should not be any difference in the systemic way among the subjects of various groups. In case of clinical research, research results will be biased, if treatment groups are systematically different. In a study examining the efficacy of a surgical intervention, suppose that subjects are assigned to two different groups: Control and treatment. The surgical intervention outcome may be influenced by an imbalance, if a larger proportion of older subjects are assigned to treatment group. The treatment effect would be indistinguishable from the impact of the covariates imbalance, thereby showcasing the need for the researcher to control the covariates in the analysis to obtain an unbiased result.[7,8]

Second, proper randomization ensures on a pre-knowledge of assignment of groups. That is, researchers, subjects, or participants, and others must not know to which group the subject is to be assigned. Trials with inadequate or vague randomization tended to overestimate the treatment effects up to 40% compared with those trials that used proper randomization.[9] The outcome of the research can be negatively influenced by this inadequate randomization.

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Statistical techniques, such as multivariate analysis of covariance (ANCOVA) or ANCOVA, or both, are widely used to adjust for imbalance of the covariate in the analysis stage of the clinical research. The interpretation of the postadjustment approach is often difficult because covariate imbalance frequently results in unanticipated interaction effects, like unequal slopes among subgroups of the covariates.[4] The slopes of regression lines are the same for each group of covariates, which is considered as one of the major assumptions in ANCOVA. The adjustment needed for each group of covariate may vary, which is troublesome because to adjust the outcome variable, ANCOVA uses the average slope across the groups. Hence, the ideal way to balance covariates among groups is to apply sound randomization in the design stage of a clinical research instead of that after the data collection. In such cases, the random assignment is needful and guarantees validation of the statistical tests of significance that are used for comparing the treatments.

TYPES OF RANDOMIZATION

Several procedures have been proposed for the assignment of participants randomly to different treatment groups in clinical trials. The present article gives a brief review of common randomization techniques like simple randomization, stratified randomization, block randomization, and covariate adaptive randomization. The advantages and disadvantages of every method are described. Selecting a method that will produce interpretable and valid results for your study is very important. Use of online randomization software to generate randomization plan using block randomization procedure will be presented.

SIMPLE RANDOMIZATION

It is a randomization technique based on a single sequence of random.[1] Complete randomness of the assignment of a subject to a particular group is maintained. The most basic method of simple randomization is flipping a coin. An example of the two faces of a coin (heads – control, tails – treatment) and two treatment groups (control *vs* treatment) can determine the assignment of each subject. Various other methods include throwing dice, e.g., =< 3 – control, > 3 – treatment or a shuffled pack of cards, e.g., odd – treatment, even – control. For subjects of simple randomization, random numbers which are computer generated or a random number table found in a statistics book can also be used.

This is a simple and easy randomization approach to implement in a clinical research. In a clinical research with large number of subjects, this method can be trusted to generate similar numbers of subjects among the groups. Though, randomization results can be problematic in a clinical research with relatively small sample size, which results in an unequal number of participants among the groups.

BLOCK RANDOMIZATION

This method is designed to randomize the subjects into different groups that result in equal sample sizes. It is used to ensure a balance in the sample size across groups over period. Being small and balanced with predetermined group assignments to blocks, keeps the number of subjects in each group similar at all the times.[1] Researcher determines the size of the blocks, which should be a multiple of the number of groups; e.g., with two treatment groups, block size should be either 4, 6, or 8. Blocks are mostly used in smaller increments as researchers can more easily control the balance.[10]

After the determination of the block size, all possible balanced combinations of the assignment within that block, i.e., an equal number for all groups within the block is to be calculated. Then the blocks are randomly chosen to determine the assignment of the subject to groups.

Even though sample size balance may be achieved using this method, rarely comparable groups in terms of certain covariates may be generated. For example, one group may negatively influence the results of the clinical trial by having more participants with secondary diseases like diabetes, hypertension, multiple sclerosis, cancer, etc., that could create a confounding bias of the existing data. Pocock and Simon[11] stressed on the importance of controlling these covariates because of the serious consequences which are to be faced during the interpretation of the results. Such an imbalance could result in introducing bias in the statistical analysis and in turn reduces the power of the study. Hence, covariates and sample size must be balanced in any clinical research.

STRATIFIED RANDOMIZATION

This method addresses the need to balance and control the influence of covariates. It is used to achieve balance among the groups in terms of baseline characteristics or covariates of the subject. The researcher who understands the potential influence that each covariate is having on the dependent variable must identify specific covariates. Stratified randomization is achieved by the generation of separate blocks for each combination of covariates, where subjects are assigned to the appropriate block of covariates. After the identification of subjects and their assignment to blocks, the technique of simple randomization is employed within each block to assign subjects to one of the groups.

This method controls for the possible influence of covariates that would jeopardize the conclusions of the clinical research. A clinical research for different rehabilitation techniques following a surgical procedure will have many covariates. It is clear that the rate of prognosis is affected by the age of the subject. Here, age could be a confounding variable and it influences the outcome of the clinical research. This method of randomization can balance the treatment and control groups for age or any other identified covariates. Even though it is a relatively simple and useful technique, especially for clinical trials with smaller sample size, if many covariates must be controlled, it becomes complicated to implement.[12] This technique has another limitation; where it works only when all subjects have already been identified before group assignment. The method is very rarely applicable because clinical research subjects are enrolled one at a time on a continuous basis. Using the technique of stratified randomization is difficult, when the baseline characteristics of all subjects are not available before assignment.[10]

COVARIATE ADAPTIVE RANDOMIZATION

A potential problem with the clinical research comprising small to moderate sample size is that imbalance of important covariates among treatment groups may result in simple randomization. Covariates imbalance is very important because of its ability to influence the interpretation of research results. This technique of randomization has been recommended by several researchers in clinical research as a valid alternative randomization method.[7,13] In this method, a new subject is subsequently assigned to a particular treatment group by taking the specific covariates and previous assignments of participants into account.[7] This randomization uses the method of minimization by the assessment of sample size imbalance among several covariates.

By using the online randomization programs, Clinstat, Minim, Stata, EDGAR, etc., a researcher can generate an accurate randomization plan for the assignment of treatment to patients.

Another online software for randomization, which is used to generate randomization schedule, is http://www.randomization.com. It comprises three randomization plan generators. The first plan generator uses the method of randomly permuted blocks and randomizes each subject into a single treatment. The second plan generator operates where subjects are to receive all of the treatments in random order and creates random permutations of treatments for situations. The third plan generator produces a random permutation of integers. It is particularly useful for selecting a sample without replacement.

First Generator

The seed for the random number generator[14,15] is obtained from the clock of local computer and is printed at the bottom of the randomization plan. Also if a seed is included in the query, where it can be used to reproduce or verify a particular plan it overrides the value obtained from the clock. A maximum of 20 treatments can be specified. Randomization plan is not affected by the order of the treatments entered or particular boxes left blank if we do not need all of them. The program starts by sorting treatment names internally. Sorting is case sensitive, hence, the same capitalization should be used for the recreation of an earlier plan. An example of 20 patients allocating into two groups (each group with 10 patients), treatment labels should be entered in the boxes specified for treatment, and the tab "Number of patients per block" should be filled up by the total number of patients that is 20 and enter the number of blocks required in the tab "Number of blocks" for more than one block for a Block randomization. The output of this online software is presented as follows (Fig. 1).

1. Control
2. Diseased
3. Control
4. Diseased
5. Diseased
6. Diseased
7. Control
8. Control
9. Diseased
10. Control
11. Diseased
12. Diseased
13. Control
14. Control
15. Diseased
16. Control
17. Control
18. Diseased
19. Control
20. Diseased

20 subjects randomized into 2 blocks
To reproduce this plan, use the seed 19564
along with the number of subjects per block/number of blocks
and (case-sensitive) treatment labels as entered originally.

Fig. 1: Output of online software with seed for 20 subjects randomized into two blocks; www.randomization.com

1. ______
   - Diseased
   - Control
2. ______
   - Control
   - Diseased
3. ______
   - Diseased
   - Control
4. ______
   - Diseased
   - Control
5. ______
   - Diseased
   - Control
6. ______
   - Control
   - Diseased
7. ______
   - Control
   - Diseased
8. ______
   - Diseased
   - Control
9. ______
   - Diseased
   - Control
10. ______
    - Diseased
    - Control

10 subjects randomized into 1 block
to reproduce this plan. use the seed 25125

Fig. 2: Output of online software with seed for 10 subjects randomized into two groups in single block randomization; www.randomization.com

Second Generator

In this design, up to six treatments can be permuted. Suppose treatments are called A, B, C,…. If there are two treatments, the treatments can be ordered (permuted) in two ways AB and BA. For three treatments, the possible number of permutations are six: ABC, BAC, ACB, CBA, CAB, and BCA. Generally, when we consider "k" treatments, the treatments can be ordered in k! ways. This technique has its major application in split-mouth design. The split-mouth design is mostly used in oral health research. In a split-mouth study, either the right or left halves of the dentition is assigned by each of two treatments randomly. The effectiveness of the design is that it removes a lot of interindividual changeability from the estimates of the effect of treatment (Fig. 2).

CONCLUSION

There are several benefits of randomization. In the experiment, it ensures against the accidental bias created and produces comparable groups in all respect except the intervention received by each group. The purpose of this paper is to introduce the concept of randomization, elaborating its significance and to review several techniques of randomization to guide the researchers and practitioners to design their randomized clinical trials in a better way. For benefit of researchers, use of randomization online has been effectively demonstrated in this study. Simple randomization works effectively for small to moderate sample size clinical trials when n is less than 100 without the covariates and the clinical trials with large sample size, i.e., when n is greater than 100. For the clinical trials with small to moderate size, which have several prognostic factors or covariates, the method of adaptive randomization would be more useful in providing a means to achieve treatment balance.

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