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An overview of randomization techniques: An unbiased assessment of outcome in clinical research

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Abstract

Randomization as a method of experimental control has been extensively used in human clinical trials and other biological experiments. It prevents the selection bias and insures against the accidental bias. It produces the comparable groups and eliminates the source of bias in treatment assignments. Finally, it permits the use of probability theory to express the likelihood of chance as a source for the difference of end outcome. This paper discusses the different methods of randomization and use of online statistical computing web programming (www.graphpad.com/quickcalcs or www.randomization.com) to generate the randomization schedule. Issues related to randomization are also discussed in this paper.

Keywords: Block, graphpad quickcalc, patient, randomization

INTRODUCTION

A good experiment or trial minimizes the variability of the evaluation and provides unbiased evaluation of the intervention by avoiding confounding from other factors, which are known and unknown. Randomization ensures that each patient has an equal chance of receiving any of the treatments under study, generate comparable intervention groups, which are alike in all the important aspects except for the intervention each groups receives. It also provides a basis for the statistical methods used in analyzing the data. The basic benefits of randomization are as follows: it eliminates the selection bias, balances the groups with respect to many known and unknown confounding or prognostic variables, and forms the basis for statistical tests, a basis for an assumption of free statistical test of the equality of treatments. In general, a randomized experiment is an essential tool for testing the efficacy of the treatment.

In practice, randomization requires generating randomization schedules, which should be reproducible. Generation of a randomization schedule usually includes obtaining the random numbers and assigning random numbers to each subject or treatment conditions. Random numbers can be generated by computers or can come from random number tables found in the most statistical text books. For simple experiments with small number of subjects, randomization can be performed easily by assigning the random numbers from random number tables to the treatment conditions. However, in the large sample size situation or if restricted randomization or stratified randomization to be performed for an experiment or if an unbalanced allocation ratio will be used, it is better to use the computer programming to do the randomization such as SAS, R environment etc.[1–6]

REASON FOR RANDOMIZATION

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Researchers in life science research demand randomization for several reasons. First, subjects in various groups should not differ in any systematic way. In a clinical research, if treatment groups are systematically different, research results will be biased. Suppose that subjects are assigned to control and treatment groups in a study examining the efficacy of a surgical intervention. If a greater proportion of older subjects are assigned to the treatment group, then the outcome of the surgical intervention may be influenced by this imbalance. The effects of the treatment would be indistinguishable from the influence of the imbalance of covariates, thereby requiring the researcher to control for the covariates in the analysis to obtain an unbiased result.[7,8]

Second, proper randomization ensures no a priori knowledge of group assignment (i.e., allocation concealment). That is, researchers, subject or patients or participants, and others should not know to which group the subject will be assigned. Knowledge of group assignment creates a layer of potential selection bias that may taint the data.[9] Schul and Grimes stated that trials with inadequate or unclear randomization tended to overestimate treatment effects up to 40% compared with those that used proper randomization. The outcome of the research can be negatively influenced by this inadequate randomization.

Statistical techniques such as analysis of covariance (ANCOVA), multivariate ANCOVA, or both, are often used to adjust for covariate imbalance in the analysis stage of the clinical research. However, the interpretation of this post adjustment approach is often difficult because imbalance of covariates frequently leads to unanticipated interaction effects, such as unequal slopes among subgroups of covariates.[1] One of the critical assumptions in ANCOVA is that the slopes of regression lines are the same for each group of covariates. The adjustment needed for each covariate group may vary, which is problematic because ANCOVA uses the average slope across the groups to adjust the outcome variable. Thus, the ideal way of balancing covariates among groups is to apply sound randomization in the design stage of a clinical research (before the adjustment procedure) instead of post data collection. In such instances, random assignment is necessary and guarantees validity for statistical tests of significance that are used to compare treatments.

TYPES OF RANDOMIZATION

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Many procedures have been proposed for the random assignment of participants to treatment groups in clinical trials. In this article, common randomization techniques, including simple randomization, block randomization, stratified randomization, and covariate adaptive randomization, are reviewed. Each method is described along with its advantages and disadvantages. It is very important to select a method that will produce interpretable and valid results for your study. Use of online software to generate randomization code using block randomization procedure will be presented.

Simple randomization

Randomization based on a single sequence of random assignments is known as simple randomization.[3] This technique maintains complete randomness of the assignment of a subject to a particular group. The most common and basic method of simple randomization is flipping a coin. For example, with two treatment groups (control versus treatment), the side of the coin (i.e., heads - control, tails - treatment) determines the assignment of each subject. Other methods include using a shuffled deck of cards (e.g., even - control, odd - treatment) or throwing a dice (e.g., below and equal to 3 - control, over 3 - treatment). A random number table found in a statistics book or computer-generated random numbers can also be used for simple randomization of subjects.

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

Block randomization

The block randomization method is designed to randomize subjects into groups that result in equal sample sizes. This method is used to ensure a balance in sample size across groups over time. Blocks are small and balanced with predetermined group assignments, which keeps the numbers of subjects in each group similar at all times.[1,2] The block size is determined by the researcher and should be a multiple of the number of groups (i.e., with two treatment groups, block size of either 4, 6, or 8). Blocks are best used in smaller increments as researchers can more easily control balance.[10]

After block size has been determined, all possible balanced combinations of assignment within the block (i.e., equal number for all groups within the block) must be calculated. Blocks are then randomly chosen to determine the patients' assignment into the groups.

Although balance in sample size may be achieved with this method, groups may be generated that are rarely comparable in terms of certain covariates. For example, one group may have more participants with secondary diseases (e.g., diabetes, multiple sclerosis, cancer, hypertension, etc.) that could confound the data and may negatively influence the results of the clinical trial.[11] Pocock and Simon stressed the importance of controlling for these covariates because of serious consequences to the interpretation of the results. Such an imbalance could introduce bias in the statistical analysis and reduce the power of the study. Hence, sample size and covariates must be balanced in clinical research.

Stratified randomization

The stratified randomization method addresses the need to control and balance the influence of covariates. This method can be used to achieve balance among groups in terms of subjects' baseline characteristics (covariates). Specific covariates must be identified by the researcher who understands the potential influence each covariate has on the dependent variable. Stratified randomization is achieved by generating a separate block for each combination of covariates, and subjects are assigned to the appropriate block of covariates. After all subjects have been identified and assigned into blocks, simple randomization is performed within each block to assign subjects to one of the groups.

The stratified randomization method controls for the possible influence of covariates that would jeopardize the conclusions of the clinical research. For example, a clinical research of different rehabilitation techniques after a surgical procedure will have a number of covariates. It is well known that the age of the subject affects the rate of prognosis. Thus, age could be a confounding variable and influence the outcome of the clinical research. Stratified randomization can balance the control and treatment groups for age or other identified covariates. Although stratified randomization is a relatively simple and useful technique,

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especially for smaller clinical trials, it becomes complicated to implement if many covariates must be controlled.[12] Stratified randomization has another limitation; it works only when all subjects have been identified before group assignment. However, this method is rarely applicable because clinical research subjects are often enrolled one at a time on a continuous basis. When baseline characteristics of all subjects are not available before assignment, using stratified randomization is difficult.[10]

Covariate adaptive randomization

One potential problem with small to moderate size clinical research is that simple randomization (with or without taking stratification of prognostic variables into account) may result in imbalance of important covariates among treatment groups. Imbalance of covariates is important because of its potential to influence the interpretation of a research results. Covariate adaptive randomization has been recommended by many researchers as a valid alternative randomization method for clinical research.[8,13] In covariate adaptive randomization, a new participant is sequentially assigned to a particular treatment group by taking into account the specific covariates and previous assignments of participants.[7] Covariate adaptive randomization uses the method of minimization by assessing the imbalance of sample size among several covariates.

Using the online randomization http://www.graphpad.com/quickcalcs/index.cfm, researcher can generate randomization plan for treatment assignment to patients. This online software is very simple and easy to implement. Up to 10 treatments can be allocated to patients and the replication of treatment can also be performed up to 9 times. The major limitations of this software is that once the randomization plan is generated, same randomization plan cannot be generated as this uses the seed point of local computer clock and is not displayed for further use. Other limitation of this online software Maximum of only 10 treatments can be assigned to patients. Entering the web address http://www.graphpad.com/quickcalcs/index.cfm on address bar of any browser, the page of graphpad appears with number of options. Select the option of “Random Numbers” and then press continue, Random Number Calculator with three options appears. Select the tab “Randomly assign subjects to groups” and press continue. In the next page, enter the number of subjects in each group in the tab “Assign” and select the number of groups from the tab “Subjects to each group” and keep number 1 in repeat tab if there is no replication in the study. For example, the total number of patients in a three group experimental study is 30 and each group will assigned to 10 patients. Type 10 in the “Assign” tab and select 3 in the tab “Subjects to each group” and then press “do it” button. The results is obtained as shown as below (partial output is presented)

Another randomization online software, which can be used to generate randomization plan is http://www.randomization.com. The seed for the random number generator[14,15] (Wichmann and Hill, 1982, as modified by McLeod, 1985) is obtained from the clock of the local computer and is printed at the bottom of the randomization plan. If a seed is included in the request, it overrides the value obtained from the clock and can be used to reproduce or verify a particular plan. Up to 20 treatments can be specified. The randomization plan is not affected by the order in which the treatments are entered or the particular boxes left blank if not all are needed. The program begins by sorting treatment names internally. The sorting is case sensitive, however, so the same capitalization should be used when recreating an earlier plan. Example of 10 patients allocating to two groups (each with 5 patients), first the enter the treatment labels in the boxes, and enter the total number of patients that is 10 in the tab “Number of subjects per block” and enter the 1 in the tab “Number of blocks” for simple randomization or more than one for Block randomization. The output of this online software is presented as follows.

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CONCLUSION

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The benefits of randomization are numerous. It ensures against the accidental bias in the experiment and produces comparable groups in all the respect except the intervention each group received. The purpose of this paper is to introduce the randomization, including concept and significance and to review several randomization techniques to guide the researchers and practitioners to better design their randomized clinical trials. Use of online randomization was effectively demonstrated in this article for benefit of researchers. Simple randomization works well for the large clinical trails (n>100) and for small to moderate clinical trials (n<100) without covariates, use of block randomization helps to achieve the balance. For small to moderate size clinical trials with several prognostic factors or covariates, the adaptive randomization method could be more useful in providing a means to achieve treatment balance.

Footnotes

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