

Fundamentals of Randomization in Clinical Trial

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Abstract The randomized control trial (RCTs) is widely accepted to be the best design for evaluating the efficacy of new therapies, and thus it is accepted as the gold standard to evaluate treatment effects. Random assignment of patients to the treatment ensures the internal validity of the comparison of new treatment with a control group. Unfortunately, the randomization process in most research studies is not implemented properly. The purpose of this review is to provide researchers and scholarly clinicians with a better understanding of different options to achieve proper randomization. The information presented in this article will also help to better design and interpret the results of clinical trials. Therefore, a brief definition of randomization plus its concise benefits in clinical trials, and the processes of an accurate randomization procedure, generation of unpredictable random allocation sequence and allocation concealment are considered. Recommendations are made to select the suitable techniques of generation of random allocation and allocation concealment. Finally, the authors describe how the appropriate implementation of these two procedures reduces the potential for biases throughout the study and improves the power of the study.

Keywords *Allocation Concealment; Study Power; Randomized Control Trial; Random Allocation*

1. Introduction

Randomized controlled trial (RCT) is defined as a clinical trial in which the participants are assigned randomly to different treatments groups. Thus, each participant has a known and equal chance of being assigned to a given group, and the group assignment cannot be predicted. Randomized experimental design is the preferred method of research for evaluating treatment effects in health research since it provides the highest degree of control over a research study and allows the researcher to draw causal inferences with the highest degree of confidence [1]. They use a systematic methodology that allows controlling for confounder variables [2]. In real life, clinical experiments never control for all confounders; however, RCT design offers the most convincing evidence of the effect of one variable has on another [3].

Most health research journals have been increasingly interested in publishing the results from RCTs [4]. The increasing recognition toward using randomized control trials (RCT) in health care started in the 20th century. In the 1920s, randomized control trial was developed by R.A Fisher to be a fundamental of experimental design [5] in agricultural research [6]. Later, in the 1940s, owing to the

advocacy of Sir Austin Bradford Hill, the RCT design was promoted in health care. His efforts resulted in using the random allocation of an experimental trial and after publishing his results, randomization became known as a secure experimental design to avoid bias in between group comparisons [7].

In RCTs, randomization refers to the use of the probability theory used to assign subjects to different treatment groups. It is a method, based on chance alone, by which the study participants are assigned to the various treatment groups being studied. Randomization minimizes the differences among groups by equally distributing participants with particular characteristics among all the trial arms. It is a curial procedure in RCTs without which the treatment effect could be overestimated by up to 41% [8]. Results from randomised and non-randomised studies could generate completely opposing results [8]. Unpredictable random allocation sequence is a crucial factor that requires attention when implementing any randomized control trial. The process of concealing the randomization until at least all the participants are assigned to their groups is the most important component of randomization without which the randomization fails in a trial [9]. Contrasting and combining results from different studies have demonstrated that the treatment effect is exaggerated with inadequate or unclear random allocation and allocation concealment [10]. We are unaware of a suitable article that comprehensively discusses the benefits and procedures of these two crucial elements of randomization (random allocation and allocation concealment) together, which is necessary to give a comprehensive understanding appreciation for the randomization process. In addition, this article outlines the benefits of using randomization, describes its characteristics, and provides examples of how to perform proper sequence generation and allocation concealment. Finally, discussions in which how proper randomization and allocation procedures reduce biases and increase the study's power are performed. Thus, the content of this paper will help researchers in the area of health sciences to understand how randomization and allocation concealment operate and decrease several flaws regarding knowledge when analyzing, criticizing, and designing future trials.

2. Benefits of Randomization

According to Altman et al. [11], randomization has three major advantages. First, it eliminates bias in the assignment of treatments (selection bias). Second, random allocation facilitates masking the identity of treatments to investigators, participants, and evaluators. Third, randomization allows the use of probability theory and increases the likelihood that changes in the dependent variable are attributable to the independent variables rather than extraneous factors or confounding variables; thus, it decreases the possibility of confounding bias. Randomization tends to distribute individual differences equally across the groups, so that the groups differ systematically in only one way: the intervention being examined in the study. Randomization reduces the chance of any systematic error; for example, let's suppose that the study of a specific rehabilitation technique after osteoarthritis-surgery is intended. A subject could be assigned to two different groups: to a new rehabilitation technique and to a control group. When subjects with good health condition are intentionally or unintentionally (non-randomly) channelled to treatment groups, biases infiltrate to the study. Randomization uses probability theory to ensure that a specific patient will not be consciously or unconsciously assigned to the desirable group to receive a specific intervention. In this case, avoiding the introduction of bias in group assignment helps to ensure that difference in outcome between treatment groups is merely due to chance [7]. Above all else, randomization helps to equally distribute participants with particular characteristics (covariates) among all the trial treatment arms; while non-randomized trials may lead to covariate imbalances in clinical trials. Covariate imbalances can be adjusted in the data analysis stage by statistical methods such as the analysis of covariance (ANCOVA). Although ANCOVA uses the average across the slopes of subgroups to adjust the covariate effect on outcome, different subgroups of the covariate may have different slopes which could be problematic if there is imbalance in the distribution between subgroups. Proper randomization should prevent this problem by equally distributing participants with various covariates among the treatment groups [12].

The success of randomization depends on two interrelated aspects in clinical practice: adequate generation of an unpredictable allocation sequence and concealment of that sequence until assignment occurs. Thus, the person enrolling participants does not know in advance which treatment the next person will get. This is called “allocation concealment”.

3. Generation of Allocation Sequence's

To minimize bias in a study, researchers should randomly assign each participant to the various treatment groups. There are different types of random allocation techniques used to achieve the desire of an unbiased study. The three most predominant techniques that deliver true randomized allocation are: simple, block, and stratified randomization. These will be the focus of the next section. Then, the less accurate but more pragmatic method, covariate adaptive randomization, along with the other randomization techniques will be discussed.

3.1. Simple Randomization (Un-Restricted Randomization)

Simple randomization is a kind of randomization procedure that is based on a single sequence of random assignments [13]. Simple randomization preserves complete unpredictability for each intervention assignment, and no other allocation method surpasses the bias prevention and unpredictability of this method. Simple randomization involves assembling a sample in such a way that each independent and same-size subset within a population is given an equal chance of being allocated to the various groups [14].

Simple randomization could be generated by coin-tossing, dice throwing, and dealing with previously shuffled cards which represent reasonable approaches for the generation of a simple complete randomization sequence. These are the manual methods of drawing lots. Owing to the threat to randomness, difficulties in implementation, and lack of an audit trail, the use of these methods is not recommended, and investigators are advised to avoid the use of manual procedures [7]. Other methods such as computer random generators or table of random numbers may be used. These options represent reliable, easy, unpredictable, and reproducible approaches that provide an audit trail [7]. Unless the researchers report clearly the randomization method that was used, study results should be treated with caution. When researchers report the use of either a computer random number generator or a table of random numbers, the reader can be more confident that the randomization process was adequate with the sequence generation approach [7].

Simple randomization is problematic when using small sample sizes ($n < 100$) since the sequence can be predicted, and disproportionate sample sizes per group can be obtained [15]. For example, randomizing a total sample size of 10 to two groups using a coin-toss, simple randomization procedure might yield to unequal groups (ratio imbalance) of 7 participants to the control and 3 to the treatment group (Figure 1) [4, 7]. For these reasons, simple randomization is not recommended for trials of less than 200 subjects [14].

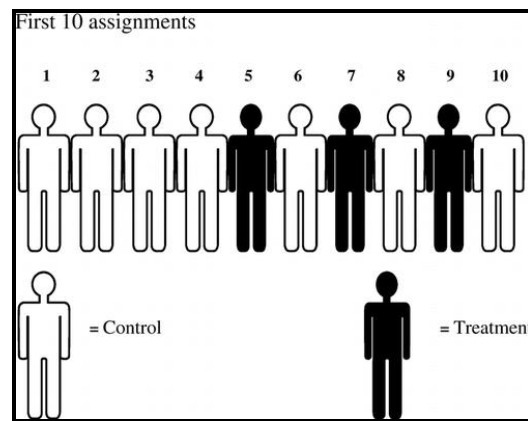
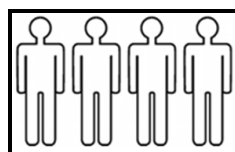


Figure 1: Imbalance Sample Size due to Simple Randomization in Small Groups (N=10)

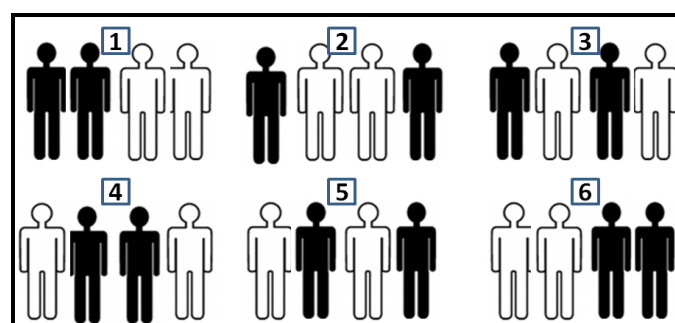
3.2. Permuted-Block Randomization or Blocked Randomization (Restricted Randomization)

The restricted randomization procedure is a useful method to control to the likelihood of obtaining an allocation sequence with an undesirable sample size [16]. In other words, restricted randomization is recommended to use in small randomized control trials when the researchers want treatment groups of equal sizes. It attempts to obtain an unbiased study and yield comparison groups with equal sample size throughout the trial [15]. Permuted blocks or blocking is the most commonly used method to attain balanced randomization. A “blocked size” or “the allocation ratio” is specified and the subjects are allocated within each block [7]. The block size is determined by the researcher a priori and should be the multiple of the number of treatment groups. For example, with two treatment groups, block sizes of 4, 6, and 8 would be appropriate. The “allocation ratio” is the ratio of the number of subjects in one group versus the other group. After specifying the block size, all the potential contribution of the assignments within each group must be calculated, and then the blocks are randomly chosen to determine the assignment of all participants. For example, with a total of 20 participants randomized to two treatment groups, a randomized block method would be: (A) block size is four, (B) possible balance combinations with two T1 (Treatment one) and two T2 (Treatment two) in each block are calculated as 6 and (C) where each block is randomly chosen to determine the assignment of all 20 participants (Figure 2).

(A) Block Size



(B) Possible Balance Combination (e.g. 2 to Treatment 1, and 2 to Treatment II)



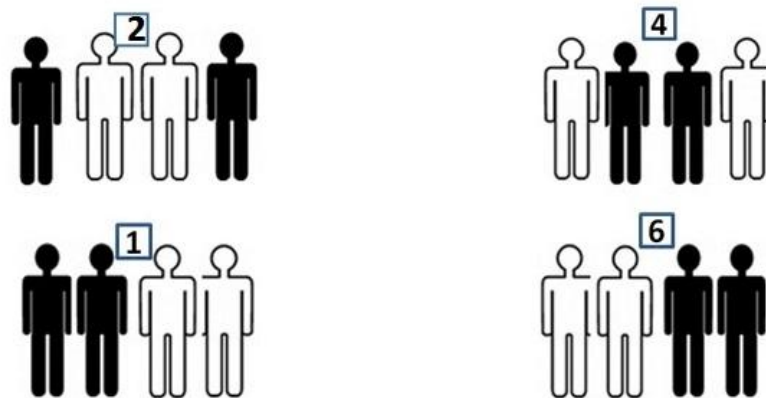
(C) Random Selection of Blocks (E.G. 2, 1, 3, 4, 6) to Assign All the 20 Participants

Figure 2: Balance Sample Size Produced with Block Randomization Even with Small Sample Size ($n=20$)

The block size may remain fixed throughout the trial or may change randomly. Whenever blocked randomization is used in a trial that is not double-blinded and the block size is less than 6, it should be varied to reduce the chance of deciphering the assignment scheme by those who are responsible for recruiting the participants. This avoids the risk that sequence is recognized when the treatment allocation becomes known after the assignment based on recognition of past assignments, resulting on inadvertent introduction of selection bias. This is of particular concern when small block sizes are used. To preserve unpredictability of the allocation sequence, the use of a large block size (e.g. 10 or 20 instead of a small block size) and the random variation of block size are recommended [17]. When blocking is used, details regarding the block size (or sizes if varied), allocation ratio, and the random method of the selection at the final stage (e.g. computer random number generator or random number table) must be clearly reported. This allows the reader to be certain about the unpredictability of the random sequence [7].

3.3. Stratified Randomization

There is also a possibility that certain prognostic factors influence the study results. To control these covariates, investigators need to use the stratified randomization method to generate a random sequence [7]. This method helps to achieve balance among groups in terms of participants' covariates (characteristics). To reap the benefits of randomization, specific covariates must be identified by investigators who are knowledgeable about the potential effect of each covariate on a dependent variable a priori. Then, to do the stratification, investigators should generate separate blocks for the combination of each covariate and assign each participant to appropriate blocks of covariate. Finally, simple randomization should be done within each block to assign each participant to one of the treatment groups [4].

As previously mentioned, results of trials can be endangered by influence of the possible covariates. To adjust for this problem, investigators may use the stratified randomization method [7]. For example, when examining the effect of different rehabilitation techniques after a certain surgery, there are a numbers of covariates that influence the result of the trial. It is believed that the patients' age has an effect on the rate of healing and mortality. Therefore, age might be a confounding variable in this case as it influences the outcome of the study. Using stratified randomization, investigators can balance the control and treatment groups for age, sex, and other similar covariates [4].

Suppose we want to perform a stratified randomization with our sample based on gender (2 levels: female/male) and age (2 levels: under 50/above 50) having 2 groups and total of 30 participants. With the combination of 2 covariates, stratification results in 4 blocks. Then a simple randomization procedure, such as coin-tossing, is needed within each block to assign the participants to one of the treatment groups (Figure 3).

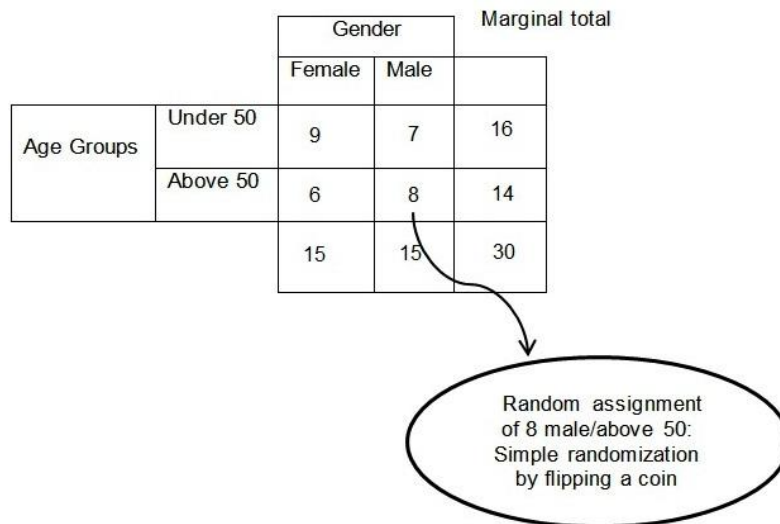


Figure 3: Scheme of the Stratified Randomization Which Controls the Covariates of Gender and Age between Treatment Groups. It Results 4 Blocks, and the Participants Within Each Block will be Assigned to the Treatment and Control Group by Flipping a Coin to Have an Equal Sample Sizes Terms of Covariates

As discussed, one of the major benefits of randomization is that it can avoid severe imbalances of the most important prognostic factors across groups and make the groups comparable in terms of covariates [17]. It may also present an ample quantity of balance (on the stratified factors) and may yield slightly more statistical power and precision [17]. Besides the aforementioned advantages, using stratified randomization in small clinical trials is relatively simple. However, in large trials with more stratified covariates to control, the complexity of the trial makes stratified randomization less useful [7]. Using too many block combinations may lead to a large number of blocks and small participant numbers within each block, potentially resulting in large imbalances in the overall treatment allocation. As a general guide, it is believed that if the number of blocks moves towards one half of the sample size, balance in covariates tends to fail [18]. Regarding the number of participants for a trial, although there is no absolute cut-off, trials with more than 200 subjects probably do not benefit from stratification [19]. For these purposes, in small studies in which the number of stratification is more than 1 or 2 covariates, the number of blocks can rapidly move toward the number of participants and reduce the usefulness of the procedure to balance the participants [13]. Finally, using stratified randomization is very difficult, because it requires baseline characteristics for all participants, and all participants must be identified before group assignment, which is difficult, as in clinical research trials participants are often enrolled one at a time on continuous basis [14].

3.4. Covariate Adaptive Randomization

Covariate adaptive randomization has supporters [20] and detractors [14]. Although many research studies have suggested using covariate adaptive randomization in clinical trials as means of achieving a valid randomization [4, 21], it is not as usable as the simple, block, or stratified randomization methods [7, 22]. Using this method, only the first subject's assignment is, in fact, selected at random [23]. For remainder newly enrolled subjects, the probability of being assigned to a particular group

varies. The newly recruited subjects are sequentially assigned to a particular group by considering the specific covariate and the previous assigned group [12, 24]. This happens in order to make small groups closely similar with respect to several characteristics [7] and reduce the covariate imbalances [14].

The covariate adaptive approach was first described by Taves [25]. To use Taves' covariate adaptive randomization method, researchers should look back to the examination of previous participant group assignments and then assign each individual, who is newly enrolled in the study, by making a case-by-case decision on group assignment [25].

Consider again the example of 2 groups involving 30 participants, with gender (2 level: male/ female) and age (2 level: under 50/ above 50) as covariates, when enrolment in the trial is being done in a continuous manner. The five participants are already assigned from which the first participant is assigned by flipping the coin, then a newly enrolled participant number 6 who is under 50 and female needs to be assigned to one of the treatment groups, either 1 or 2. Taking into account the characteristics of the 6th participant and using Taves' method, the marginal totals of the corresponding covariate categories for each group must add together. Then, the participant will be assigned to a group with the lowest covariate to decrease imbalance. Since in this example the total number of participants randomized to Treatment 2 is lower than Treatment 1 ($2 < 3$), the 6th participant is assigned to Treatment 2 (Figure 4).

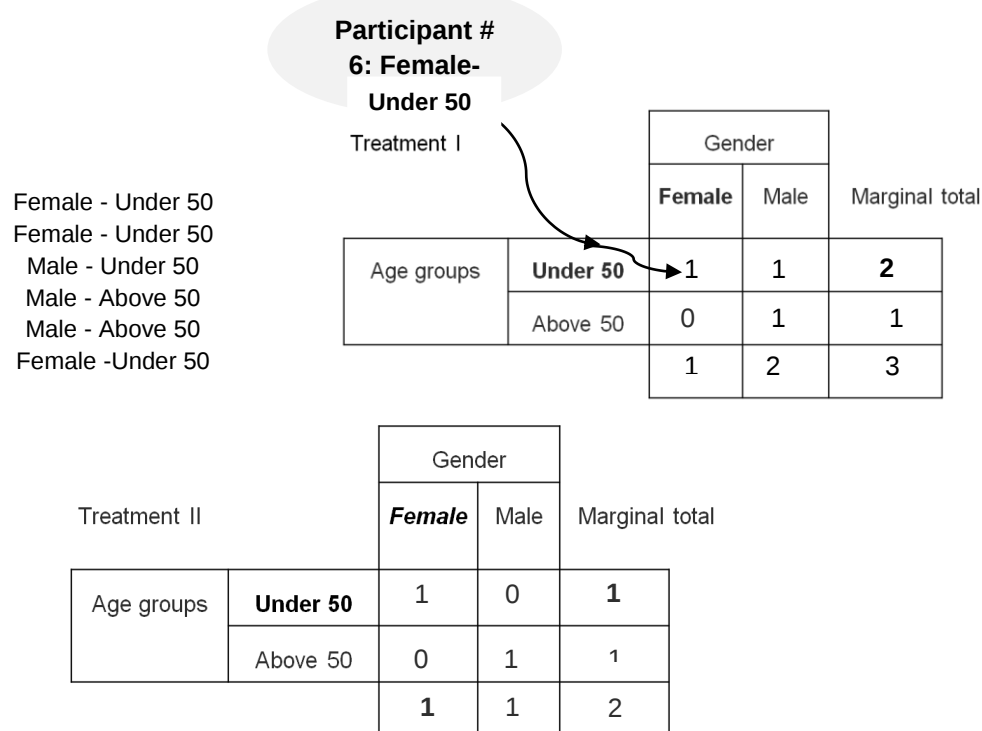


Figure 4: Schematic of the First 5 Participants' Group Assignments by Two Covariates (Gender and Age) and Assigning of the Newly Enrolled (6th) Participant Who will be assigned to the Treatment II into the Block of Female/Under 50

4. Summary of Random Allocation Sequence

In summary, to select a proper randomization method, researchers must consider several factors including sample size, balance in sample size, covariates, and participant enrolment. For large sample sizes ($n > 200$), simple randomization is a good choice. Block randomization, however, is desirable when the balance in sample size is required. To reach the balance in baseline

characteristics, stratified randomization is suggested. Covariate adaptive randomization can achieve better balance than other methods when participants are continuously enrolled into a study [4]. Figure 5, which is adapted from the study by Kang et al., (2008) [4] describes the best method selection process clearly.

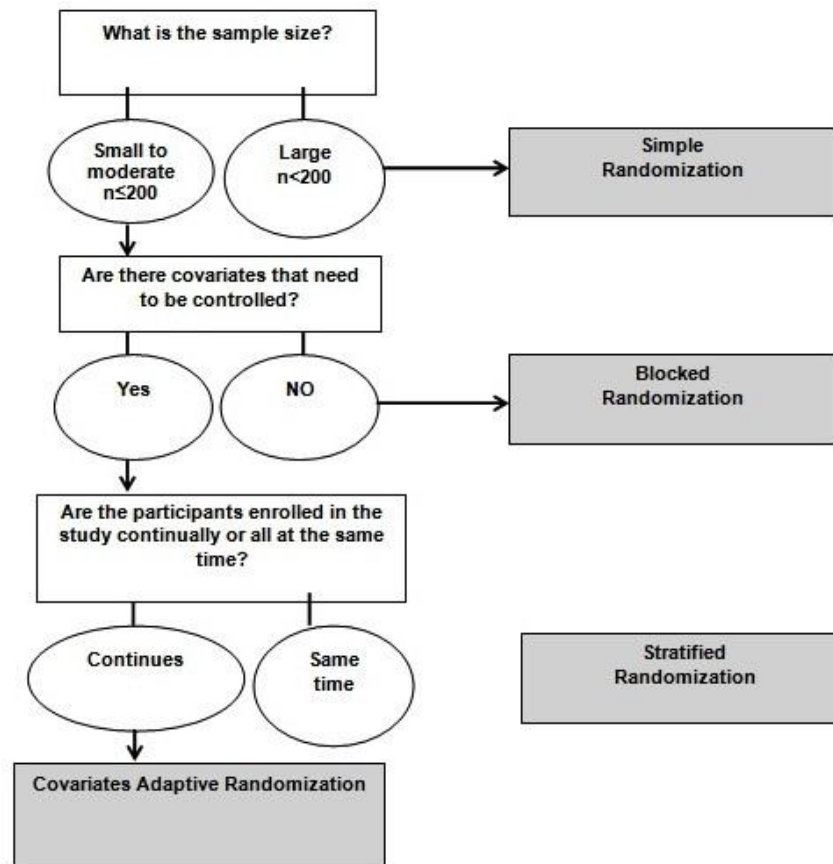


Figure 5: Flowchart for Selecting a Proper Randomization Technique. Appropriate Techniques are indicated in Gray Boxes. Adapted from Kang et al., 2008

5. Allocation Concealment

Randomization is a chain of procedures that consists of the generation of a random sequence and allocation concealment. Although the process begins with sequence generation, it does not finish until all the subjects are actually assigned to the groups. Therefore, the process of allocation concealment and the proper implementation of randomization must follow the generation sequence [26]. Allocation concealment keeps clinicians, participants, investigators, and everybody involved in a trial unaware of upcoming assignments [9]. No matter which randomization technique is used (e.g. simple random, stratification) to randomly allocate each participant to a group, if one of the members involved in the trial is able to identify the upcoming assignment the value of randomization is compromised [27,28]. Allocation concealment is a term used for the implementation of the sequence [27], not for the generation of it. Moreover, most researchers confuse allocation concealment with the blinding of treatment [27, 29]. While allocation concealment is always possible, blinding is not always feasible [30] and is considered after assigning the participants. If the researcher is aware of the next assignment, he/she may intentionally or unintentionally influence the selection of participants. For example, if researchers or health care providers know that the upcoming assignment would be an exercise treatment, he/she may tend to influence who is randomized next by selecting a specific participant who may need more exercise. Besides, when the subject becomes aware of the allocation

scheme, knowledge of allocation to control or placebo group may cause the subject to withdraw from the study or to wait to ensure assignment to the active treatment [26]. Therefore, the prognosis of the upcoming allocation group introduces bias that the designed randomization was supposed to eliminate. Some standard methods of ensuring allocation concealment include: sequentially numbered, opaque, sealed envelopes, pharmacy controlled, numbered or coded containers, and central randomization from which the centralized assignment protocol does not involve any person associated with the research trial [26, 31]. Before using this method, researchers should screen each patient to ensure that they meet the eligibility criteria before they call to the randomization center to receive the treatment assignment. It is clear that by using this method neither the patients nor the researchers are able to predict the next allocation; then one can feel more confident about the results of the study [9].

Pharmacy controlled, numbered or coded containers, and central randomization methods require a broad infrastructure support that may be beyond the resources available to investigators in single-center trials [13, 32]; therefore, sequentially-numbered, opaque, sealed envelopes are considered easy and complete methods to implement, but are susceptible to manipulation. Herbison et al. (2011) [33] found through a meta-epidemiological approach that sealed envelopes with some form of enhancement (opaque, sequentially numbered, and so forth) may give adequate concealment when compared with more sophisticated methods of allocation concealment. Hence, to do a secure opacity researchers are recommended to carefully develop and supervise the allocation process to conserve concealment. Thus, researchers should ensure that all the envelopes are numbered beforehand and opened in sequence, after the participants' name and other information is written on each envelope in detail. Using carbon paper to transfer written information to the allocation paper, inside the envelope, generates a valuable unbiased appraisal trial. It is also recommended to use foil inside envelop and around the carbon copy and allocation paper to make randomization completely safe from being deciphered [7, 13, 32]. Finally, it would be best if different persons perform different parts of the event to decrease the chance of predicting sequences and assignments and introducing bias to the study (30). A proper sequence of procedures using opaque concealed envelopes is shown in Figure 6.

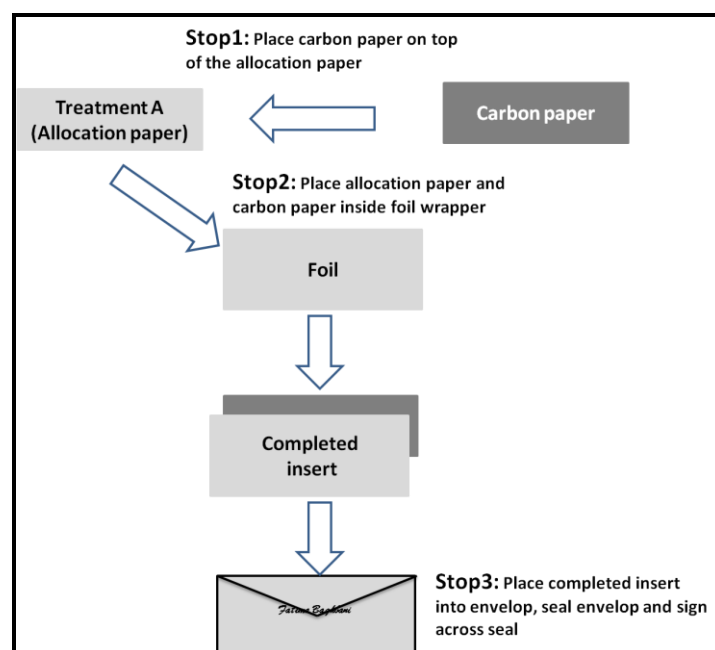


Figure 6: Preparation of Envelop Insert – Adapted from Doig et al., 2005 [32]

6. The Effect of Randomization on Power of the Study

The power of the study is affected by many factors including the size of actual difference between the mean of treatment groups (effect size), and the amount of the error variance. As the effect size increases, the power increases; while, the greater the error variance, the less the power. Any factors that increase the error variance decrease the researcher ability to detect the true effect size [34]. When the ability of the researcher to measure the true treatment effect interferes with unwanted differences between groups (heterogeneity), due to either random error or systematic error, the internal validity of interventional trials may be threatened. The random differences between groups are unavoidable, but can be made less likely by ensuring that a study has an adequate sample size [35]. Whereas, bias or systematic error can be introduced intentionally or unintentionally and is far more likely to interfere with the study execution and interpretation of the results, and unfortunately it is much more difficult to avoid. Bias can arise at three stages of the research study: during initial enrolment of the participants, implementation of the study, and analysis of the results [35]. The next section is focused on the sources of systematic error or bias during the initial enrolment of the participants, the effect of errors on the power of the study, and how randomization can overcome these biases throughout the study.

Selection and confounding biases are common systematic errors in clinical trials [36]. Selection bias occurs when the sample is not representative of the target population. This may happen if investigators can intentionally or unintentionally preferentially enrol patients between treatment arms; consequently the bias seeps into the study [37]. Selection bias exaggerates the effect size of trials. For example, it has been shown that inadequate allocation concealment can overestimate treatment effects on average by 18% [27, 38]. This has been confirmed by several researchers in different areas of health science [39, 10]. However, other research failed to see the association between allocation concealment and effect size [40, 41]; findings of a met-epidemiological study demonstrated a possible reason for this inconsistency is the type of intervention or outcome assessments. They demonstrated that effect size was exaggerated by inadequate allocation concealment and lack of blinding just in trials with subjective measures and All-cause mortality outcomes [38]. Other factors such as method of randomization have also been shown to influence the results of trials and can potentially inflate type I error to 100% that leads to a “false positive”: the error of rejecting a null hypothesis when it is actually true [42, 43]. Effect size appears to be exaggerated when the random-sequence generation, and also the allocation concealment, is inadequate or unclear [10]. Without allocation concealment, the effects of the intervention tend to be overestimated. In fact, trials with inadequate allocation concealment yield estimates of treatment effect up to 40% larger than trials where adequate allocation concealment was achieved [9, 27]. Therefore, a large treatment effect from a “randomized” trial without adequate allocation concealment might simply reflect biased allocation. The results of a meta-analysis demonstrated that the treatment effect is exaggerated in trials with inadequate or unclear random allocation (ratio of odd ratios = 0.89 for all outcomes), and with inadequate or unclear allocation concealment versus adequate (ratio of odd ratios = 0.93 for all outcome) compared to the trials where adequate concealment was achieved [10]. Randomization can overcome selection bias by increasing block size and varying block size during allocation sequence generation, and allocation concealment [44].

Confounding bias, another common systematic bias (in clinical trial), is defined as a fake association between a factor and outcome, which is not a real factor itself and arises when the factor is related to a range of other characteristics that do increase the outcome risk. It appears when a researcher propose an exposure to an outcome, but in fact measures the effect of a third factor, termed a confounding variable [37]. This may happen if covariates (characteristics) that influence the outcome are not equally distributed between treatment groups [7]. Neglecting randomization will have no influence on the effect size if the patients are actually from a homogenous population, while it has great influence when there is significant heterogeneity in some systematic way among the participants

enrolled to the trial. Therefore, neglecting stratification or other types of restricted randomization (permuted block) may substantially distort the effect size [16]. Randomization can avoid severe imbalances of the most important covariate factors across groups and make the groups comparable in term of the covariates [17]. Therefore, it may slightly improves systematic power to measure differences between two groups, as well as precision if the out-come is correlated with the covariates for participants with significant heterogeneity [17].

The other benefit of randomization is yielding equal sample size. It is well known that, by equally distributing sample size, systematic power to measure differences between two groups improves. Therefore, effects to achieve near or exact equality of sample sizes for treatment and control groups in designs of interventional trials are increasing [45]. Although large imbalances in sample size may appear alarming, the power of a trial is not sensitive to small deviations in equality of the sample sizes [16]. However, in restricted randomization situations (e.g. stratification) group sizes do not have to be exactly equal. Thus, restricted approaches that produce similar sample sizes would yield power much the same as those that generate equal sizes provided the number of participants is slightly more than equal sample sizes [16]. For example, a trial with a number of 60:40 sample size imbalances and with 13% more subjects will have the same power as a balanced trial [46].

Randomization is currently accepted as the most important factor to objectively measure the effect of the treatment, and sets the gold standard for clinical research trials [32]. Unfortunately researchers, for unintentional reasons, fail to implement proper randomization. Common errors include: failing to describe the details regarding the methods of random allocation, concealment (or both) and once it is described, it does not appear as if the subjects were truly randomized. A study of four medical journals dealing with obstetrics and gynecology revealed that approximately 5% of the published RCT reports have assigned participants based on a non-random method [31]. This must represent a gross underestimation as 63 % of the publications failed to indicate a specific method used to generate a random sequence [31].

7. Conclusion

Since randomization is considered the gold standard in most clinical trials, the purpose of this manuscript was to introduce randomization, review several randomization techniques, and to discuss factors related to optimizing randomization procedures. This review paper may be used as a guide for researchers and scholar clinicians to better analyze, criticize, and design randomized clinical trials. Several factors lead a research study to a pure treatment effect size and increased power; randomization is one of the major factors that deserve attention in designing and carrying out clinical trials. It eliminates selection bias, ensures balance of sample size and baseline characteristics, and is an important step in ensuring the validity of statistical tests of significance used to compare treatment groups.

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