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Methods of Randomization: Overview and Application in Small Clinical Trials

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Abstract

Background: *This manuscript is a guide to help students in their preparation to design a clinical study. Randomized clinical trials are required to investigate different therapeutic approaches and their efficacy.*
Discussion: *The authors discuss the great importance of a well-applied randomization technique as a fundamental tool to increase the internal validity of a clinical study. Applying a didactic approach, we use examples of studies in different areas to demonstrate the efficacy of randomization and the different methods to perform it.*
Conclusion: *After years of study, the large numbers of benefits of randomization are unquestioned. It is a fantastic tool to fight and avoid bias, boosting statistical power to the research. For a small sample size, some different randomized methods such as stratified randomization may avoid unbalance and validate the outcomes.*

Keywords: *randomization, small studies, bias, guide, clinical trial, publication.*

Introduction

A high standard trial may be measured through the randomization technique applied in the trial. Actually, randomization is fundamental tools in studies that a researcher needs to use in order to be able assess, properly, the efficacy of different therapeutic approaches or interventions. It brings several benefits to research. Some basics ones include: elimination of selection bias; creating basis for statistical tests, which require that each participant has equal chance of receiving the intervention; and provides balance regarding known and unknown confounders among groups; and, as such, it is an accurate tool to demonstrate the efficacy of the treatment, which is been tested in that study. In research which investigators select treatment assignments, the occurrence of large biases is frequent. This is a nonrandomized trial. (1,3)

Randomization helps to avoid selection and accidental bias. Researchers need to discuss the design of a study with their peers before defining the best tool for each trial. (1,2)

However, due to ethical concerns, some trials, in surgical areas, may obtain more benefits from observational design, which, by definition, do not include randomization in the design. (25)

Although randomization is an important method to apply in clinical trials, it is not all the time an easy technique to be performed. (1,2,4,6)

Furthermore, randomization of the subjects in trials is very important to validate outcomes and to the valorization of the manuscript in the scientific community. (5,6,8)

Creation of a randomization schedule is very important in a clinical trial as well as the choice for a more effective and reproducible technique. This schedule must include randomizing numbers of each subject or treatment options and the same condition for the assigning random numbers. For instance, in studies with small sample size, randomization can be obtained by using the random number in the schedule to the treatment conditions for assigning the random numbers. However, despite of the virtual advantages, due to the small sample size, the risk of imbalanced groups is high with potential invalidation of the outcomes. (7,9,10)

Discussion

Why Randomization?

In 1926, the concept of randomization was first introduced by Fisher, in an agricultural study. He brought

to the academic community the importance of randomization as a tool for unbiased studies when comparing treatment groups.

Several reasons reinforce the use of randomization in life science research. Initially, subjects in different groups should not differ in any study. Nevertheless, more frequently in small studies, imbalances in some variables, for instance, gender, is not unusual. It is one of the causes of bias in research outcomes. (4,18)

Second, to avoid selection bias it is important no a priori knowledge of group assignment, i.e., allocation concealment. For that, subjects and researchers should not be informed in which group participants will be allocated. (11,12)

Other frequent occurrence is a presence of imbalance in prognostic variables such as age, (e.g. older subjects assigned to the treatment group compared to the control, which, in clinical or surgical research, might compromise the accuracy of the results due imbalance). This imbalance makes it imperative to the researcher adjust baseline covariates in the statistical analysis to get an accurate treatment effect estimate. (4,11,12,18) Statistical techniques such as analysis of covariance (ANCOVA), regression model and multivariate ANCOVA are launched to adjust the covariate imbalance in the study. However, these tests may allow adjustments, but those are done posteriorly, which is not the ideal scenario. The best way to avoid imbalance is assuring randomization as well as having a good study design. In other words, those tests mentioned above don't completely solve the issue of imbalance, as they frequently leads to unanticipated interactions effects among subgroups of covariates.

Despite of all statistical risks noted above, randomization in assignment is very important and may guarantee the validity of studies. (11,12,13)

How to do randomization?

Randomization offers to each subject the same chance of being assigned to either intervention or control group. Neither, the subjects nor the investigator should know which is the treatment group before the assignment of subjects. This is an important approach to avoid selection bias. Researchers should keep their minds that bias is one of the most dangerous "threats" to the study validity. (6,14)

There are some options to perform randomization. The main methods include: (15,16).

1. Simple Randomization;
2. Replacement Randomization;
3. Block Randomization (random permuted blocks);
4. Biased Coin;
5. Stratified Randomization;
6. Minimization (method of adaptive randomization);
7. Stratifying by Institution;

Other randomization methods are:

8. Pre-Randomization;
9. Response-Adaptive Randomization (play-the-winner);
10. Unequal Randomization.

Randomization provides balanced groups, with comparable known and unknown risk factors, increasing the validity of statistical tests. (4,14)

Methods of randomization include phone call to central office or scaled envelopes (14,15,16) Another major aspect is eligibility criteria. Researchers need to verify whether subjects enrolled meet eligibility, according to inclusion and exclusion criteria, before carry out randomization. Also, randomization should be performed as close as possible to treatment time to avoid death or withdrawal before treatment start.

1. Simple Randomization: "Simplicity vs. Imbalanced groups"

This method is based on a "single" sequence of random assignments.

There are different methods to perform it such as:

- Toss a coin (H [heads] = intervention; T [Tail] = control);
- Generate a random digit (use a random starting point, a calculator or computer program: even#= intervention; odd#= control; or 0 to 4= intervention; 5 to 9= control).
- Alternating assignment (e.g. ABAB…). However, it should not be used once there is no random component; investigator knows next assignment.

Toss a coin is the most common and basic method, it is based on flipping a coin to determinate the assignment of the subjects.

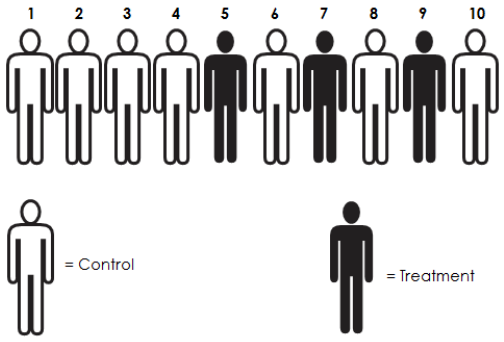

Figure 1 Imbalance of sample size between treatment arms due to simple randomization (coin toss) in a small trial (n = 10)

Other possibilities are: flipping a die (less than or equal to 3= control; over 3= treatment); shuffled deck of cards (even= control; odd= treatment). (9,8,14)

Through the simple randomization method, the subject has 50% of chance to be allocated in treatment or control group. It is a very feasible option when researchers have a small staff, short time window or limited budget. This kind of strategy is commonly applied as it usually does not compromise statistical inference of the study as the chances that the next subject be allocated in either group is not affected by the allocation of the previous participant. However, in small sample size, the risk of imbalanced groups is high, for instance, resulting in an unequal number of subjects among groups. (9,10,14,15) (Figure 1)

2. Replacement Randomization

This is a type of design in which, if necessary, a new randomization may be performed before the start of the treatments.

In a clinical trial, it is important to define previously the amount of imbalance that would be unacceptable. For instance, if after the initial randomization there is a meaningful difference in the number of subjects between groups that compromises the comparability between them, it is possible to perform new simple randomization to achieve the desirable equipoise. If the expected balance was not found, new randomization lists may be created before the study starts, until an acceptable one is obtained. (15,16)

3. Block Randomization

This method is designed to define the randomization of the subjects into groups with equal sample size (1:1). This kind of technique is applied to allow a balance in sample size among groups over time (method may be helpful in reducing imbalance among groups). Blocks may have different sizes and need to be balanced with predetermined group assignments. Therefore, it is a good method to use in small sample size studies. (14)
However, regarding other covariates, for instance level of physical activity and severity of disease, this method would not eliminate the total possibility of imbalance. Although balance in sample size may be ensured with this approach, groups are rarely comparable regarding specific factors. For instance, groups may differ with regards to comorbidities such as diabetes, cancer, hypertension, etc, which may cause negatively influence over the outcomes of the study. Notwithstanding this argument, because block sizes can randomly vary a bit, the possibility of unblinding during allocation of patients is smaller. The size of the blocks should be similar and, also, it should be a multiple of the number of groups (for example in two treatment groups, block size of either are 4 or 6). Hence, block randomization method produces balanced study arms, even with a small sample size. (Table 1) (15,17,18)

Table 1 Block randomization recommendations

Block randomization
• With block randomization, where b = block size, the number in each group never differs by more than b/2 ⇒ This ensures treatment balance through whole accrual period.
• Blocking factor, b, should **not** be known to investigators (if known, the last treatment in each block is predictable).
• A trial without further stratification should have a fairly large block size (say, b = 10 to 20) to reduce predictability.
• Do **not** use blocks of size 2.
•Block size can be varied over time, even **randomly**.

4. Biased Coin

Biased coin design is a method to determine the balance of achieves averaging and how much variation is experienced from one simulation to the next.

If simple or blocking randomization is used on as few as one or two covariates, it may cause imbalance between groups, compromising the results and validity of the trial. Studies with a small sample size (small sampling populations or trials in early phases) can apply an adaptive randomization tool, such as biased coin method, as an approach to obtain balance between groups regarding a number of covariates. (12,14)

Some of pros factors in this method are: Next assignment to the groups cannot be predicted and statistical power is greater with equal allocation.

Practical example:

When the number of patients is already on each group of treatment (n_1 and n_2) and it is equal ($n_1 \approx n_2$), then randomize to both of treatment with P = ½.
If $n_1 > n_2 + C$, then increase P (treatment 2) to be > ½.
If $n_2 > n_1 + C$, then increase P (treatment 1) to be > ½.
(C + unacceptable level of imbalance between group sizes)
Larger P □arger P ceptable level of imbalance be

- Suggested P ≈ 2/3

5. Stratified Randomization

Stratified randomization design is applied to trials that need to control and balance the influence of covariates. (Table 2) In fact, with this method other designs usually need to be associated to create an appropriate block of covariates. The block size should be small to preserve balance in small strata. It is important to assure that the entire imbalance is not important.(10,14) In studies with many strata, predictability should not be a problem. (19,20).

Table 2 Example of three stratification factors

		Treatment A	Treatment B
Gender	Male	16	14
	Female	10	10
Age	≤ 40	13	12
	41 to 60	9	6
	≥ 61	4	6
Disease stage	Stage I	6	4
	Stage II	13	16
	Stage III	7	4
Total		**26**	**24**

- Gender (2 levels)
- Age (3 levels)
- Disease stage (3 levels)

Especially in small studies, the imbalance may be significant and stratified randomization may improve balance among confounders and potentially prognostic factors. Stratification is important to prevent Type I Error and advance power for small trials. Very large trials (> 500 patients) may not require stratification. (10,13,14,15) In stratification method, subjects are randomized in strata of important covariates that might influence significantly the results. (Figure 2) Another important aspect is minimizing all covariates influence before randomization. It is not advisable to do during the data analysis. (14,20)

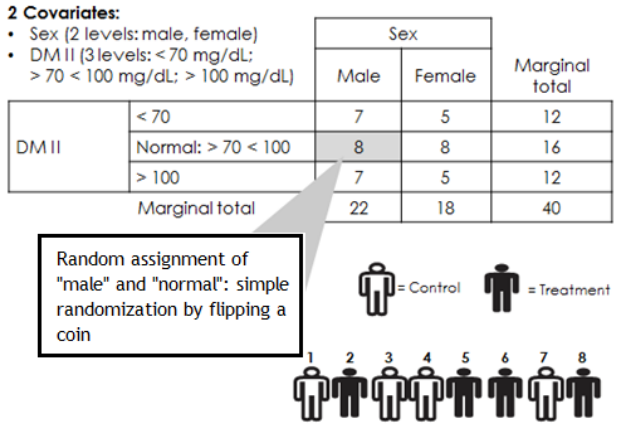

Figure 2 Stratified randomization procedure produces equalized study groups that are balanced by covariates

When occurs the presence of different levels of the same covariate (e.g., severe, moderate and light pain), it is important considerer dichotomizing this covariate. (10,14, 17). Covariates, if unbalanced, may threat trials conclusions; so stratified randomization method would prevent this occurrence. (14,18). For example, in a study, age of patients could be a confounding variable and might influence the result of the trial.

Stratified randomization has an important limitation: it will be a useful technique when all subjects have been identified prior to the group assignment. When baseline data of all patients are not available before the assignment, is very difficult to apply stratified randomization. This method is very complicate to use if many covariates must be controlled too.(14,18,20)

6. Minimization (Adaptive Randomization)

This method of randomization allows that patients are change or a new participant is assigned to one of the groups, during the trial progress. Adaptive randomization uses a method of minimization by assessing the imbalance of sample size caused by several covariates. Taves first described minimization method in 1974. It is a very important method to avoid imbalance because allows approach and examination of each previous subject group assignment. (Table 3) (20,21)

Table 3 Minimization

Minimization
• Balances treatments simultaneously over several prognostic factors (strata).
• Does not balance within cross- classified stratum cells; balances over the marginal totals of each stratum separately.
• Is used when the number of stratum cells is large relative to sample size (stratified design would yield sparse cells).
• Can be computerized.

Similar to the method described above the Pocock and Simon covariates adaptive randomization. The main difference is the temporary assignment of subjects to the groups based on the absolute differences amid groups to define the assignment of the participants in each group. This method also indicates using of a variance management. Instead of calculating absolute difference among groups, this method can calculates the variance among treatment groups. For instance, including new patient to the group: first, assign this new participant temporarily to control group resulting in a marginal total in this group; second, calculating the absolute difference among control and treatment group and sum it; third, temporarily assign the new participant to the treatment group resulting in marginal total to the different variables between groups; fourth, assign this new participant to the control group too. This is necessary because of the lowest sum (in small sample sizes) of absolute differences. (4,20,22)

Frane applied a covariate adaptive randomization for both continuous and categorical variables, for instance, in regression and ANOVA, modeling the response as a function of predictors. Frane used *P* values to identify imbalance among treatment groups. This method includes: 1. Temporarily assigning the participant to the control and treatment groups; 2. Calculating *P* values for each of covariates using *t* test and analysis of variance (ANOVA) for continuous variables; 3. Determinate the minimum *P* value for control or treatment groups; 4. Assign the participant to the group with the large

minimum *P* value to try to avoid more imbalances among groups. (4,20,22)

Covariate adaptive randomization can be used effectively to balance meaning covariates between control and treatment groups. This method can obtain fewer imbalances than other habitual randomization tools and better manipulate the problem of increasing numbers of covariates. However, when the number of blocks approaches half part of the sample size, the balance of covariates with this method can star to fail. (4,20,17,22)

7. Stratifying by Institution

Multi-center clinical trial is broadly as the better way to obtain the ideal study to validate data to benefit trial which aboard treatment drugs or new modalities of treatment. Randomization is essential to avoid varieties of bias. Even using the minimization method, add institution, as a stratification factor is not a problem.
Utilizing random permuted blocks within strata and adding institution, as a stratification factor, will probably lead to sparse components. (24)

Other randomization methods

8. Pre-randomization

Basically, this method determinates that subjects first be submitted to randomization and assign to each group (treatment or control) and then approach the patients to ask for informed consent to participate in the trial. Statistician Marvin Zelen described it and some studies denominate this method as Zelen's Design. (4,15,24)

In this method subjects who were allocated on the standard treatment group do not need to be consented for the participation (private issues). Of course, subjects randomized to experimental group needs to go through the informed consent form. However, these patients can decline and receive the standard treatment. For best results in a pre-randomized study, the proportion of patients who refuses the randomized treatment must be significantly small (less than 10%). Otherwise, additional sample size will be required to compensate for those who refuse the randomized treatment. (25,26)

Pre-randomization design is applied to boost the accrual of subjects. However, it may failure to approach subjects as assigned, leading to the necessity for even more subjects.

9. Response-Adaptive Randomization (Play-the-Winner)

In this method patients are "randomized" according and based on the response of the previous subject. For instance: to the first patient, toss a coin. If the response to this first subject is positive, then the second patient receives the same allocation and treatment. (4,12,15,25,29) (Table 4)

Table 4 Toss a coin

If response = success (S), then second subject receives the same treatment.

Stay with the winner until a failure (F) is observed. At failure, assign next subject to other treatment. For example:

Patient #	1	2	3	4	5	6	7	8	...
Treatment A	S	F				S	F		
Treatment B			S	S	F			S	

Play-the-Winner (PW) method receives better application if patient response is determined very fast.

The "pros" to this method include that more patients can receive the better treatment. The "cons" are: investigator knows the next assignment; it may lead to loss of statistical power when final sample size is quite unequal. (24,25,27)

The majority of researchers and statisticians recommend PW randomization if the investigator has a strong assurance that the new treatment of the study has more effectiveness than conventional therapy before the beginning of the trial.

Although PW is an interesting design, it is controversial and not commonly used because it has a lot of issues associated and other biases can be introduced over time. (27,28,29)

10. Unequal Randomization

Generally, in randomized controlled trials, equal sample size in each group can maximize statistical power of the study. On the other hand, the use of unequal randomization ratio in the groups can produce a significant reduction of the power. This will occur if the ratio is 3:1 or more. For example, randomizing with ratio 2:1, the power decreases from 0.95 to 0.925 what means not much loss. (Figure 3) Moderately use of unequal randomization is statistically feasible and may be useful in phase II trials. Some reasons for unequal randomization include for instance: to gain greater experience when using a new treatment; to improve accrual if the expectative with a new treatment is high; and to confer a trial great financial savings due a low cost. (15,17).

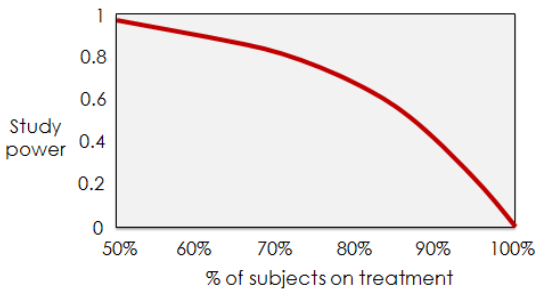

Figure 3 Reduction in power of a trial as the proportion on the new treatment is increased. Power with equal allocation is 0.95

Conclusion

Following years of studies, the large numbers of benefits of randomization are unquestioned. It is a fantastic technique to fight and avoid bias and boost statistical power to the research. In small sample size, some different randomized method (Figure 4) as stratified randomization can avoid unbalance and validate the outcomes.

Actually, almost in all of the areas of research, randomization is an important tool for further upward appreciation and reliability of trials results.

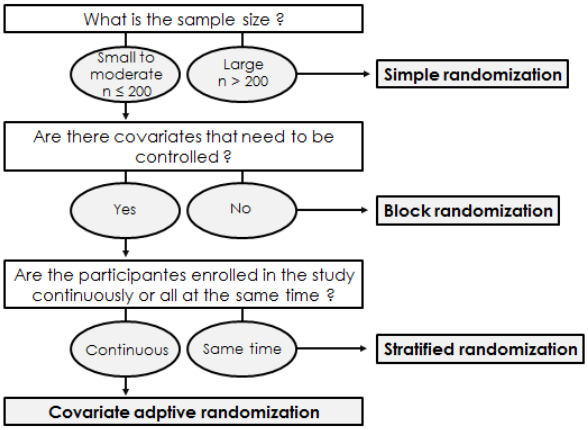

Figure 4 Flowchart for selecting appropriate randomization technique. The gray boxes represent appropppriate techniques.

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