



## Randomization and Randomized Control Trial

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### ABSTRACT

Randomized control trial (RCT) is most simplest and powerful tools in clinical research. In this, participants are assigned by chance to different groups of interventions for comparison. By assigning participants to different intervention groups by chance, it gives objective comparison between the interventions and the researcher can control the exposure to intervention using different randomization techniques. If randomization is done properly in randomized control trial, it reduces unauthentic causality and bias. We review the types of randomized control trial with special emphasis on techniques used for randomization to get proper outcomes of randomized control trials.

**Keywords:** Randomization, intervention, randomized control trial, clinical trials.

### INTRODUCTION

Randomized Controlled trial (RCT) is a type of clinical trial – most commonly used in obtaining information about adverse drug reactions and/or adverse effects of treatments and efficacy or effectiveness of new interventions in healthcare services and health technologies like medicine, nursing, pharmaceuticals, medical devices or surgery.

The terms "Randomized Control Trial" and "randomized trial" are often used synonymously, but some authors distinguish between "Randomized Control Trial" which compare treatment groups with control groups not receiving treatment (as in a placebo-controlled study), and "randomized trials" which can compare multiple treatment groups with each other.<sup>1</sup>

The randomized controlled trial is one of the simplest but most powerful tools of research. It is a study in which people are allocated at random to receive one of several clinical interventions.<sup>2</sup> Credit for the modern randomized trial is usually given to Sir Austin Bradford Hill.<sup>3</sup> Since Hill's pioneering achievement, the methodology of the randomized controlled trial has been increasingly accepted, and the number of randomized controlled trials reported has grown exponentially. The term "intervention" refers to treatment and in its much wider sense includes prevention strategies, screening programs, diagnostic tests, interventional procedures, educational models and the setting in which health care is provided.<sup>2</sup>

#### Importance of Randomization in Randomized Controlled Trial

Randomization procedure gives strength to randomized controlled trial. Randomization is the random allocation of treatment, which means all participants have the same chance of being assigned to each of the study groups.<sup>4</sup> The allocation, therefore, is not determined by the investigators, the clinicians, or other study participants.<sup>2</sup>

The purpose of random allocation of participants is to assure that the characteristics of the participants are as likely to be similar as possible across groups at the start of the comparison. If randomization is done properly, it reduces the risk of a serious imbalance that could influence the clinical course of the participants.

There are two adequate methods of randomization – (I) Fixed allocation randomization and (II) Adaptive randomization

#### I. FIXED ALLOCATION RANDOMIZATION

In fixed allocation randomization, each participant has an equal probability of being assigned to either treatment or control and the probability remains equal throughout the study.<sup>5-9</sup>

Fixed allocation randomization is of three types:

##### A. Simple (Complete) randomization

Simple randomization is the most elementary form of randomization<sup>6</sup> in which investigator flips a coin each time a participant is eligible to be randomized and determines whether the participant goes into the intervention or control group.

**Advantage:** It is easy to implement.

**Disadvantage:** There could be a substantial change at any point in the randomization using simple randomization technique especially when the sample size is small.<sup>7</sup>

##### B. Blocked (permuted) randomization and randomly permuted block design

Hill described Block randomization, sometimes called permuted block randomization, in 1951. Blocked randomization guarantees that at no time during randomization will the imbalance be large and at that certain points the number of participants in each group will be equal.<sup>5, 6, 11</sup> For e.g. For intervention group (A) and control group (B), with a fixed block size 4,



participants can be allocated in any combination such as AABB, ABAB, BBAA, ABBA, BABA or BAAB.

Another method of block randomization may also be used. In this method for randomizing the order of assignments within a block of size 4, a random number between 0 and 1 for each of the b assignments (of which half are A and the other half B) is obtained. For e.g., 4 random numbers are drawn between 0 & 1 as shown in Table 1:

**Table 1:** Block Randomization

Assignment	Random Number	Rank
A	0.058	1
A	0.523	3
B	0.7	4
B	0.201	2

The assignments then are ranked according to the size of the random numbers. This leads to the assignment order of ABAB. This process is repeated for another set of 4 participants until all have been randomized.

In randomly permuted blocks, there are different block sizes (e.g., 4, 6 and 8), and the block size and particular order of block size are selected randomly at the beginning of each block.

**Advantage:** Balance between the numbers of participants in each group is guaranteed during course of randomization. Another advantage of blocking is that if the trial is terminated before enrollment is completed, balance will exist in terms of number of participants randomized to each group.

**Disadvantage:** Analysis of data is more complicated than simple randomization. Also with fixed blocks, people involved in the trial may be able to predict the group assignment of participants being randomized at the last in the block.

### C. Stratified randomization

Stratified randomization is a blocked randomization within stratum. The main objective of stratified randomization is to achieve comparability of certain characteristics known as prognostic or risk factors<sup>5, 12, 13</sup> (for e.g., gender, ethnicity, age, socioeconomic status etc) between treatment and control groups. Stratified randomization requires that the prognostic factors be measured either before or at the time of randomization. A separate simple or blocked randomization is applied within each stratum. Usually in order to minimize imbalance, block randomization is preferred over simple randomization within the strata. If a single factor is used, it is divided into 2 or more subgroups or strata (e.g. Age 30-34 yrs, 35-39 yrs, 40-44 yrs). If several factors are used a stratum is formed by selecting one subgroup from each of them. E.g. of stratified randomization with a block size 4, suppose an investigator wants to stratify on age, gender and smoking history (Table 2.1). One possible

classification of the factors would be three 10 yrs age levels and three smoking levels. The total number of strata is the product of the number of subgroups in each factor. Thus, the design has  $3 \times 2 \times 3 = 18$  strata as shown in Table 2.2

**Table 2.1:** Stratified Randomization:

Sub groups	Age	Gender	Smoking History
	30-34 yr.	Male	Current Smoker
	35-39 yr.	Female	Ex-smoker
	40-44 yr.		Never smoked

**Table 2.2:** Stratified Randomization with block size four:

Strata	Age	Gender	Smoking History	Group Assignment
1	30-34 yr.	Male	Current Smoker	ABBA
2	30-34 yr.	Male	Ex-smoker	BBAA
3	30-34 yr.	Male	Never smoked	ABAB
4	30-34 yr.	Female	Current Smoker	BABA
5	30-34 yr.	Female	Ex-smoker	BAAB
6	30-34 yr.	Female	Never smoked	AABB
7	35-39 yr.	Male	Current Smoker	ABBA
8	35-39 yr.	Male	Ex-smoker	BBAA
9	35-39 yr.	Male	Never smoked	ABAB
10	35-39 yr.	Female	Current Smoker	BABA
11	35-39 yr.	Female	Ex-smoker	BAAB
12	35-39 yr.	Female	Never smoked	AABB
13	40-44 yr.	Male	Current Smoker	ABBA
14	40-44 yr.	Male	Ex-smoker	BBAA
15	40-44 yr.	Male	Never smoked	ABAB
16	40-44 yr.	Female	Current Smoker	BABA
17	40-44 yr.	Female	Ex-smoker	BAAB
18	40-44 yr.	Female	Never smoked	AABB

Thus participants, who were between 30 and 34 years old, male, and current smokers, that is, in stratum 1, would be assigned to groups A and B in the sequences ABBA BABA and so on. Similarly, random sequences would appear in the other strata.

**Advantages:** Stratified randomization makes two study groups appear comparable with regard to specified factors and treatment assignments are balanced at end of

every strata block. In addition, power of the study can be increased by considering the stratification in the analysis.

**Disadvantage:** Stratified randomization is not the complete solution of all potential problems of baseline imbalance. This approach is complex to implement and is inappropriate for smaller trials.

## II. ADAPTIVE RANDOMIZATION

Adaptive procedures change the allocation probabilities as the study progresses

Two types of adaptive procedures are there: (1) Baseline adaptive randomization and (2) Response adaptive randomization

### 1. Baseline adaptive randomization procedures

#### A. *biased coin randomization*

This procedure is originally discussed by Efron<sup>14</sup> and it attempts to balance the number of participants in each treatment group based on the previous assignments but does not take participant responses into consideration.<sup>15-31</sup> E.g. if after 10 randomizations, there are 7 patients assigned to intervention and 3 assigned to control, the coin toss will become biased. Then, rather than having 1/2 chance of being assigned to either condition, the next patient will be given a 2/3 chance of being assigned to the under-represented condition and a 1/3 chance of being assigned to the overrepresented one. This procedure requires keeping track of imbalances throughout the trial.

**Advantages:** Unlike block randomization, in biased coin randomization the investigator cannot determine next assignment by discovering the blocking factor.

**Disadvantage:** Biased coin randomization is not widely used, as it is very complex method.

#### B. *Urn design*

Another similar adaptive randomization method is referred as Urn design based on work of Wei and colleagues.<sup>31-35</sup> This method attempts to keep the participants randomized to each group reasonably balanced as the trial progresses. E.g., the investigator starts with an urn containing a red ball and a blue ball to represent each condition. If the first draw pulls the red ball, then the red ball is replaced together with a blue ball, increasing the odds that blue will be chosen on the next draw. This continues, replacing the chosen ball and one of opposite color on each draw.

**Advantages:** Urn design works best when final sample size is small by preventing imbalance and keeping the participants in each group reasonably close by adjusting allocation probability.

**Disadvantage:** Urn design approaches simple randomization with increasing the trial size.

#### C. *Minimization*

Adaptive stratification methods incorporate several prognostic factors in making an 'overall assessment' of

the group balance or lack of balance. Participants are then assigned to a group in a manner, which will tend to correct an existing imbalance or cause the least imbalance in prognostic factors. This method is called minimization, as imbalances in the distribution of prognostic factors are minimized.<sup>18, 36</sup> E.g. If age is a prognostic factor and one study group has more of older participants than the other does, then the allocation of next several older participants would most likely be randomized to the group that currently has fewer older participants.

**Advantages:** Minimization helps in protecting against severe baseline imbalance for important prognostic factors.

**Disadvantage:** It is difficult to carry out if large numbers of factors are considered.

### 2. Response adaptive randomization

Response adaptive randomization uses information on participant response to intervention during the course of the trial to determine the allocation of the next participant. E.g., two types of models are there, viz., the play-the-winner, and the two-armed bandit models.

**A. Play-the-winner<sup>37</sup>** procedure assigns the first participant by the toss of a coin. The next participant is assigned to the same group as the first participant if the response to the intervention was a success; otherwise, the participant is assigned to the other group. That is, the process calls for staying with the winner until a failure occurs and then switching. The following e.g. illustrates a possible randomization scheme where S indicates intervention success and F indicates intervention failure. (Table 3).

Table 3: Play the winner model

Assignment	Participant							
	1	2	3	4	5	6	7	8
Group A	S	F				S	F	
Group B			S	S	F			S

**Advantages:** In play the winner randomization method; potentially more patients receive better treatment.

**Disadvantage:** In this method, investigator knows the next assignment

**B. Two-armed bandit model** continually updates the probability of success as soon as the outcome for each participant is known. That information is used to adjust the probabilities of being assigned to either group in such a way that a higher proportion of future participants would receive the currently 'better' or more successful intervention.<sup>38</sup> The following e.g. illustrates a possible randomization scheme where S indicates intervention success and F indicates intervention failure. (Table 4)



**Table 4:** Two-armed bandit model

Assignment	Participant							
	1	2	3	4	5	6	7	8
Group A	S		S	S	S	S	S	S
Group B		F						

**Advantages:** This method attempts to maximize the number of subjects to “best” treatment.

**Disadvantage:** In two-armed bandit model, when unequal treatment numbers results, there is loss of statistical power in treatment comparison.

#### Types of Randomized Clinical Trials:

The best classification of randomized clinical trials is offered by Jadad.<sup>2</sup>

According to Jadad, randomized controlled trials can be classified as to (1) the aspects of intervention that investigators want to explore, (2) the way in which the participants are exposed to the intervention, (3) the number of participants included in the study, (4) whether the investigators and participants know which intervention is being assessed, and (5) whether the preference of nonrandomized individuals and participants has been taken into account in the designing the study.

#### (1) RCTs that explore different aspects of the interventions

It includes: (a) explanatory or pragmatic trials; (b) efficacy or effectiveness trials and (c) phase 1, 2, 3, & 4 trials.

##### (a) Explanatory or pragmatic trials

Explanatory trials are designed to know whether new interventions work and if it works how it works. Pragmatic trials on the other hand, are designed not only to determine whether the intervention works but also to describe all the consequences of the intervention and its use under circumstances corresponding to clinical practice.<sup>39</sup> Although both explanatory and pragmatic approaches are reasonable, and even complementary, they represent extremes of a spectrum, and most randomized controlled trials combine elements of both.

##### (b) Efficacy or effectiveness trials

Randomized controlled trials are also often described in terms of whether they evaluate the efficacy or effectiveness of an intervention. Efficacy refers to whether an intervention works in people who receive it, whereas effectiveness refers to whether an intervention works in people to whom it has been offered.<sup>40</sup> Efficacy trials tend to be explanatory trials, because they are designed to yield a ‘clean’ evaluation of the effects of the intervention whereas Effectiveness trials, tend to be pragmatic, because they try to evaluate the effects of the intervention in circumstances similar to those found by clinicians in their daily practice.

#### (c) Phase 1, 2, 3 & 4

Phase I studies are usually conducted after the safety of the new intervention has been documented in animal research, and their purpose is to document the safety and tolerability of the intervention in humans. Phase I studies are usually performed on healthy volunteers.

Once the intervention passes phase I, phase II begins. Typically, the intervention is given to a small group of patients, and the purpose of this study is to evaluate the efficacy of different modes of administration of the intervention to patients. Phase II studies focus on efficacy while still providing information on safety.

Phase III studies are typically effectiveness trials, which are performed after a given procedure has been shown to be safe with a reasonable chance of improving patient's conditions. Most phase III trials are randomized controlled trials.

Phase IV studies post marketing surveillance studies of the intervention, they are performed to identify and monitor possible adverse events not yet documented. It is performed after drug and device has been approved for consumer sale.

#### (2) RCTs according to participants' exposure and response to the intervention

These types of randomized controlled trials include (a) parallel, (b) crossover and (c) factorial design

##### (a) Parallel design

In this, each group of participants is exposed to only one of the study intervention. Hence, parallel design produces *between* participant comparisons. As each participant is given only one study intervention, they do not produce statistically and clinically valid results when there are only few participants in the trial.<sup>41</sup>

##### (b) Crossover design

In this, each of the participants is given all the study interventions in successive periods. The order in which the participants receive each of the study interventions is determined at random. Hence, cross over trials produce *within* participant comparisons. As each participant acts as his or her own control in crossover trials, they can produce statistically and clinically valid results with fewer participants.<sup>41</sup>

##### (c) Factorial design

In this, two or more experimental interventions are not only evaluated separately but also in combination and against a control.<sup>2</sup> For example, a 2x2 factorial design generates four sets of data to analyze: data on patients who received none of the interventions, patients who received treatment A, patients who received treatment B, and patients who received both A and B. More complex factorial design, involving multiple factors are also used depending on the need. Factorial design allows evaluation

of the interaction that may exist between two treatments.

### **(3) RCTs according to the number of participants**

Randomized controlled trials can be performed in one or many centers and can include from one to thousands of participants, and they can have fixed or variable numbers of participants. There are three types of such trials: (a) N-of-one-trial (b) Mega-trial (c) Sequential Trial (d) Fixed Size trial

#### **(a) N-of-one trials**

N-of-one trial with only one participant are basically crossover trials in which one participant receives the experimental and the control interventions, in pairs, on multiple occasion and in random order which ends in individual results and not generalized results.<sup>42</sup>

#### **(b) Mega-Trial**

Mega trial is randomized clinical trial with a simple design which includes thousands of patients from multiple centers and from different countries; and limited data collection.<sup>43</sup> These helps in obtaining increased statistical power and generalized results.

#### **(c) Sequential trial**

Sequential trial is randomized clinical trial with parallel design in which investigators continue to recruit participants until a clear benefit and comparison is observed between two interventions or no important differences between the interventions.<sup>44</sup>

#### **(d) Fixed size trial**

In a fixed trial, sample size (i.e. number of participants) are fixed using statistical methods before starting a trial. Use of statistical methods in determining sample size will help to detect a statistically and clinically significant difference between the interventions when a difference really exists.

### **(4) RCTs according to whether the investigators and participants know which intervention is being assessed**

The strategy whether the investigators and participants know which intervention is being assessed is known as 'blinding' or 'masking'. Blinding can be implemented at least six different levels in an RCT. These levels include the participants, the investigators, or clinicians who administer the interventions, the investigators, or clinicians who take care of the participants during the trial, the investigators who assess the outcomes of the interventions, the data analysts, and the investigators who write the results of the trial. Depending on the extent of blinding, RCTs can be classified as (a) open RCT, (b) single-blind RCT, (c) double-blind RCT, (e) triple-blind RCT, and (f) quadruple-blind RCT.

#### **(a) Open RCT**

In open RCT, everybody involved in the trial knows which intervention is given to each participant. E.g. of open RCT

are trials comparing different surgical interventions or trials comparing surgery with medication.

#### **(b) Single-blind RCT**

In single-blind RCT, either participants or investigators assessing the outcomes do not know the identity of the interventions. E.g., of single blind RCT are educational or surgical interventions, trials of two surgical procedure's comparison with the use of identical wound dressing and keeping investigator under blindfold to get correct assessment of the outcomes.

#### **(c) Double-blind RCT**

In double-blind RCT, both participants and investigators in charge of assessing the outcomes of the interventions are unaware of the interventions given to each participant. E.g. of double blind RCT are trials in which new interventions are compared either with standard available treatment or with placebo. Double blind RCTs, in which new interventions are compared with placebo, are called double blind, randomized placebo controlled trials, and which new interventions are compared with a standard treatment, the RCTs are called double blind active-controlled randomized clinical trial. To achieve double blinding in active-controlled trials is often difficult and requires a double dummy technique. Double dummy techniques are particularly useful when the investigators want to compare interventions that are administered by different routes or require different techniques of administration. For instance, a double blind, double dummy RCT would be the ideal study design to compare one intervention that is given as a tablet with another that is given by injection. In such a trial, the participants in one of the study groups would receive a tablet with the active drug and a placebo injection, whereas the participants in the other group would receive a placebo tablet and an injection with the active drug.

#### **(d) Triple-blind RCT**

In triple-blind RCT, three groups of individuals involved in the trial are unaware of the identity of the intervention given to each participant. Mostly it includes the participants, the investigators giving the intervention, and one of those evaluating the outcomes. This kind of trial happens very rarely.

#### **(e) Quadruple-blind RCT**

In quadruple-blind RCT, four groups of individual involved in the trial are unaware of the identity of the intervention given to each participant. Mostly it includes the participants, the investigators giving the intervention, investigators who write the results of the trial, and one of those evaluating the outcomes. This kind of trial happens very rarely.

### **(5) RCTs that take into account the preferences of non-randomized individuals and participants**

In preference trial, participants are allowed to choose their own preferred treatment from among options



offered between treatment or placebo group and any other groups. These trials are called preference trials.<sup>45,46</sup>

There are three types of preference trials - (a) Zelen design, (b) comprehensive cohort design, (c) Wennberg's trial.<sup>5-8</sup>

#### **(a) Zelen's Design**

In a trial with Zelen's design, eligible individuals are randomized before they give consent to participate in the trial, to receive either a standard treatment or an experimental intervention. Those who are allocated to standard treatment are given the standard treatment and are not told that they are part of a trial, whereas those who are allocated to the experimental intervention are offered the experimental intervention and told that they are part of a trial. If they refuse to participate in the trial, they are given the standard intervention but are analyzed as if they had received the experimental intervention.<sup>47</sup> Almost all eligible individuals are included in the trial and it allows evaluation of correct effects of experimental interventions to participants. Zelen's design has to be open trials and the statistical power of the study may be affected if more participants choose to have standard treatment.

#### **(b) Comprehensive Cohort Design**

In comprehensive cohort trial, if a participant agrees to take part in an RCT, he or she is randomized to one of the study interventions and he or she has a strong preference for one intervention, then that person is given preferred intervention but followed up as they are part of a cohort study.<sup>47, 48</sup> The outcomes are then compared with those who participated in the cohort study to observe their similarities and differences. The differences in outcome are explained by differences in the baseline characteristics of the participants in the randomized and non-randomized groups.<sup>49, 50</sup>

#### **(c) Wennberg's Design**

In Wennberg's trial eligible patients are randomized to a 'preference' group or and 'RCT' group as per their choice. The outcomes associated with each intervention in each groups are compared to see the impact of the participants' preferences on the outcome.

#### **Advantages & Disadvantages of RCT:**

##### **Advantages:**

- Randomized controlled trials are best used to examine the effect of interventions on particular outcomes such as death or the recurrence of disease.
- The act of randomizing patients to receive or not receive the intervention ensures that, on average, all other possible causes are equal between the two groups.<sup>51, 52</sup>
- Any significant differences between groups in the outcome event can be attributed to the intervention and not to some other unidentified factor.

##### **Disadvantage:**

- Randomized controlled trials are not a panacea to answer all clinical questions; for e.g., the effect of a risk factor such as smoking cannot ethically be addressed with randomized controlled trials.
- In many situations randomized controlled are not feasible, necessary, appropriate, or even sufficient to in solving important problems.<sup>2</sup>
- Randomized controlled trials are not appropriate for cancer screening, a situation in which the outcome is rare and frequently occurs only after a long delay.<sup>53</sup>
- In some cases, randomized controlled trials may not be feasible because of financial constraints or because of the expectation of low compliance or high dropout rates.

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