



ORIGINAL RESEARCH PAPER

Epidemiology

RANDOMIZATION IN CLINICAL RESEARCH: ENSURING BALANCE AND MINIMIZING BIAS

KEY WORDS: Randomization, Randomized Controlled Trial, Block Randomization, Stratified Randomization, Minimization, Adaptive Randomization, Clinical Research.

**Dr. Lakshmi
Priya K**

Dr. Usha G V

ABSTRACT

Randomization is a fundamental methodological principle of clinical trials in which participants are allocated to intervention groups using a process involving chance. Its principal purpose is to prevent systematic differences between treatment groups and thereby reduce selection bias and confounding, allowing differences in outcomes to be more confidently attributed to the interventions being evaluated. Types of randomization include block, stratified, factorial, covariate-adaptive, minimization, restricted, response-adaptive and Cluster randomization. This narrative review discusses the rationale, principles, methods, implementation, ethical considerations, advantages and limitations of randomization in clinical trials. Literature was identified through relevant methodological publications, clinical trial guidance documents, textbooks and biomedical literature, with emphasis on methodological developments and practical application. The findings were synthesized narratively according to the purpose and practical application of different randomization methods. Properly designed and implemented randomization remains central to the validity, credibility and ethical conduct of randomized clinical trials.

INTRODUCTION

Randomized controlled trials (RCTs) are among the most reliable study designs for evaluating the efficacy and effectiveness of healthcare interventions. Their methodological strength arises substantially from the random allocation of eligible participants to different intervention groups.^{1,2,3} Randomization is a statistical procedure in which assignment to treatment groups is determined by chance rather than by the preferences of investigators, participants or clinicians. Thus, each participant has a specified probability of receiving each intervention.^{4,5,6}

The development of randomization in experimental research is strongly associated with Ronald A. Fisher and his work on the principles of experimental design.⁷ A landmark application in clinical research was the Medical Research Council trial of streptomycin for pulmonary tuberculosis, reported in 1948 under the direction of Austin Bradford Hill. Patients were allocated to streptomycin plus bed rest or bed rest alone, providing an important early demonstration of the value of randomized controlled comparison in clinical research.⁸

The fundamental objective of randomization is to prevent systematic differences in prognosis from influencing treatment assignment. Proper randomization tends, on average, to distribute both measured and unmeasured prognostic characteristics between treatment groups. Consequently, treatment allocation becomes independent of characteristics that could otherwise influence the outcome.^{2,3,9} Randomization also provides the foundation for probability-based statistical inference. Because the treatment assignment mechanism is determined by chance, statistical methods can estimate the probability that an observed difference between treatment groups could have occurred by chance.^{10,11}

However, randomization should not be considered synonymous with allocation concealment or blinding. Random sequence generation determines how assignments are produced, whereas allocation concealment prevents investigators and recruiters from knowing the upcoming assignment before participant enrolment. Blinding concerns knowledge of treatment allocation after assignment. These are distinct methodological safeguards and should be addressed separately.¹

METHODOLOGY

Relevant literature Searches were conducted in PubMed/MEDLINE, Scopus, Web of Science and Google

Scholar with search terms including randomization, randomized clinical trial, allocation concealment, block randomization, stratified randomization, minimization, covariate-adaptive randomization, cluster randomization and response-adaptive randomization. Textbooks, methodological reviews, clinical trial reporting guidance and relevant primary publications were considered.

Sources were selected when they provided information regarding the principles, statistical rationale, implementation, advantages, limitations, ethical considerations or reporting of randomization. Particular attention was given to contemporary literature addressing allocation concealment, minimization, adaptive randomization and cluster-randomized trials. The information was extracted and synthesized narratively according to the purpose and practical application of each method.

WHY IS RANDOMIZATION NECESSARY?

The major purpose of randomization is to produce comparable intervention groups at baseline and reduce selection bias. If treatment allocation is determined by investigators or participants, individuals with particular characteristics may preferentially receive one intervention. Such systematic differences can confound the relationship between treatment and outcome.² Randomization reduces this problem by making treatment allocation unpredictable. When properly implemented, it tends to distribute known and unknown prognostic factors between groups. This is one of the major reasons randomization is considered a cornerstone of the randomized clinical trial.^{2,3}

Consider a trial evaluating a new drug for hypertension. If younger participants are preferentially allocated to the intervention group and older participants to the control group, a greater reduction in blood pressure in the intervention group may reflect age-related differences rather than the treatment effect. Randomization reduces the likelihood of such systematic imbalance.

Randomization also provides a statistical basis for inference. Because the treatment allocation mechanism is known, the probability of obtaining the observed difference, or a more extreme difference, under the randomization distribution can be evaluated.⁷

Importantly, randomization does not guarantee that treatment groups will be identical at baseline. Chance imbalances can occur, particularly in small studies. Therefore, baseline

balance should be regarded as a probabilistic consequence of randomization rather than an absolute requirement.⁵

METHODS OF RANDOMIZATION

1. SIMPLE RANDOMIZATION

Simple randomization is the most basic method of treatment allocation. It uses a single random sequence, with each participant having a specified probability of assignment to each treatment group.^{1,2} For a two-arm trial with a 1:1 allocation ratio, computer-generated random numbers can be used to assign participants to intervention A or intervention B. The principal advantage of simple randomization is its unpredictability. It is straightforward to implement and is particularly suitable for large clinical trials.² However, in small studies, simple randomization may produce unequal numbers of participants between treatment groups and may result in chance imbalance in important prognostic factors.^{9,10} Therefore, although simple randomization is statistically attractive because of its unpredictability, investigators may choose restricted methods when maintaining numerical or prognostic balance is particularly important.¹¹

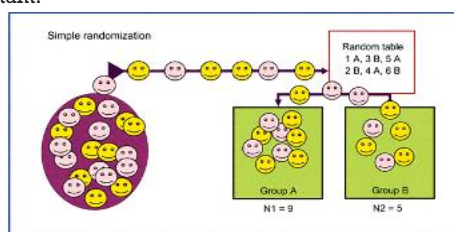


FIG 1: SIMPLE RANDOMIZATION

BLOCK RANDOMIZATION

Block randomization is a restricted randomization method designed to maintain approximate balance in the number of participants assigned to each treatment group throughout recruitment.^{9,10,11}

For a two-group trial using blocks of four, each block contains two assignments to intervention A and two to intervention B. The order within each block is randomized. Possible sequences include AABB, ABAB, ABBA, BAAB, BABA and BBAA.⁹

Block randomization is useful when the sample size is small or moderate, recruitment occurs over a prolonged period, equal numbers between groups are desirable and several centres are recruiting participants. The major disadvantage is predictability when a fixed block size is known. For example, if three assignments within a block of four are known, the fourth assignment can be predicted. Such predictability can compromise allocation concealment and introduce selection bias. Variable block sizes can therefore be used to reduce predictability. The block size should also remain concealed from investigators involved in recruitment.

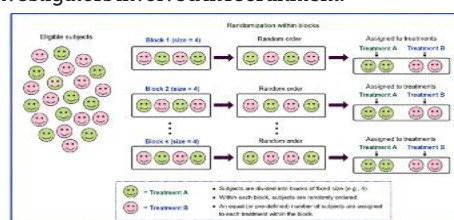


FIG 2: BLOCK RANDOMIZATION

STRATIFIED RANDOMIZATION

Stratified randomization is used when specific baseline characteristics are expected to have an important influence on treatment outcome. Participants are first classified into strata according to selected prognostic factors, and randomization is then performed separately within each stratum.¹²

A clinical trial could stratify participants according to sex, disease severity, age category, treatment centre and baseline disease status.

The principal purpose is to reduce imbalance in important known prognostic factors. Stratification may be particularly useful in small clinical trials, where chance imbalances can have a substantial influence on the observed treatment effect. A major limitation is increasing complexity when many prognostic factors are included. If two binary variables and one three-level variable are used, they may generate $2 \times 2 \times 3 = 12$ possible strata. Some strata may then contain very few participants. Therefore, select only clinically important prognostic factors.

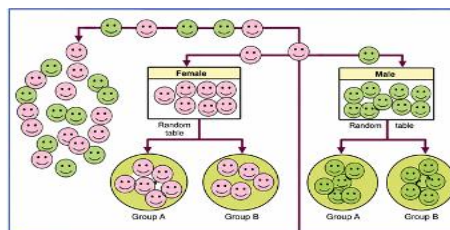


FIG 3: STRATIFIED RANDOMIZATION

FACTORIAL RANDOMIZATION

A factorial design allows investigators to evaluate two or more interventions or factors simultaneously.⁹

For example, a 2×2 factorial trials may evaluate intervention A and intervention B simultaneously. Participants can be assigned to:

1. A + B
2. A + no B
3. no A + B
4. no A + no B.

This approach can improve efficiency because it allows researchers to obtain information about more than one intervention within a single study population. However, factorial designs require careful consideration of possible interactions between interventions. If the effects of one intervention depend substantially on the presence or absence of the other, interpretation becomes more complex.

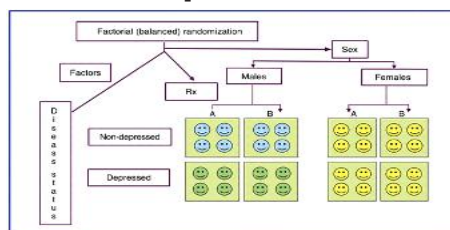
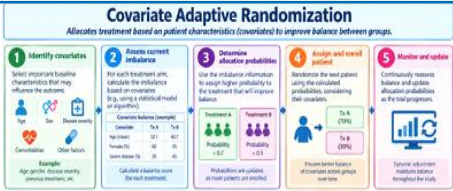


FIG 4: FACTORIAL RANDOMIZATION

COVARIATE-ADAPTIVE RANDOMIZATION

Covariate-adaptive randomization uses information about participants' baseline characteristics and previous treatment assignments when allocating subsequent participants.^{5,13} The objective is to reduce imbalance in important prognostic covariates between treatment groups. For example, suppose that after several participants have been enrolled, one group contains considerably more participants with severe disease than the other. A covariate-adaptive procedure may increase the probability that a subsequent participant with severe disease is allocated to the other group. This method can be advantageous in small and moderate-sized studies where imbalance in important prognostic factors may influence interpretation. However, it is more complex than simple randomization and requires prespecified algorithms and appropriate statistical expertise.⁹

FIG 5: COVARIATE ADAPTIVE RANDOMIZATION



MINIMIZATION

Minimization is a covariate-adaptive method developed to achieve balance across selected prognostic characteristics. The method was originally described by Taves in 1974.¹⁴ The first participant may be allocated using a random procedure. For subsequent participants, the treatment assignment is selected according to which allocation would result in the greatest overall balance in specified prognostic factors.^{15,16} Potential factors may include age, sex, disease severity, smoking status, socioeconomic status and recruitment centre. Minimization can be particularly useful when a trial has a moderate sample size, several important prognostic factors or multiple centres. A recent methodological evaluation concluded that minimization can be useful particularly when there are several major prognostic factors, multiple centres of different sizes or moderate sample sizes.⁸ However, because minimization can make future assignments more predictable than simple randomization, it should include an appropriate random element and must be implemented with strong allocation concealment.

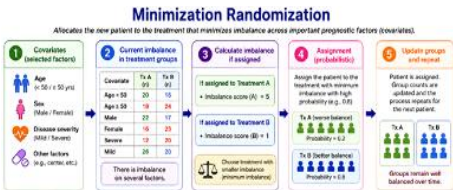


FIG 6: MINIMIZATION RANDOMIZATION

CLUSTER RANDOMIZATION

In a cluster-randomized trial, groups rather than individual participants are randomly allocated. Clusters include schools, dental clinics, hospitals, villages, communities and healthcare practices. Cluster randomization is appropriate when the intervention is delivered at the group level or when individual randomization would result in substantial contamination between participants.^{17,18,19}

For example, if an oral-health education programme is delivered to an entire school, individual randomization of children within the same school could result in information sharing between the groups among children.^{20,21} Randomizing schools rather than individual children may therefore be more appropriate. However, individuals within the same cluster tend to have correlated outcomes. This correlation is measured using the intracluster correlation coefficient (ICC). Because of this clustering, the effective sample size is smaller than the total number of individuals, and sample-size calculations must account for the design effect.^{22,23}

The design effect can be expressed as: Design effect = 1 + (m - 1) ρ where m is the average cluster size, and ρ is the intracluster correlation coefficient. Cluster trials therefore require appropriate sample-size calculations and statistical analyses that account for clustering.

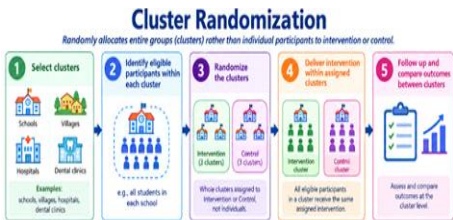


FIG 7: CLUSTER RANDOMIZATION

RESPONSE-ADAPTIVE RANDOMIZATION

Response-adaptive randomization modifies allocation probabilities according to accumulating outcome information. Thus, unlike fixed randomization, the probability of assigning a participant to a treatment can change during the trial according to observed responses.⁵

One historical approach is the randomized play-the-winner rule, introduced by Wei and Durham. Under this approach, successful treatment responses can increase the probability that subsequent participants receive the same treatment. The potential ethical rationale is that more participants may be assigned to treatments showing better responses. However, response-adaptive procedures involve substantial statistical complexity. Important considerations include the timing of outcome assessment, delayed responses, time trends, missing data, sample-size imbalance, statistical power, control of type I error and operational implementation.^{6,7} Recent literature indicates renewed interest in response-adaptive randomization, particularly within adaptive and platform trials, but its practical implementation remains limited, and reporting is often incomplete. Therefore, response-adaptive randomization should be prespecified and evaluated through appropriate statistical methods and simulation before implementation.^{24,25}

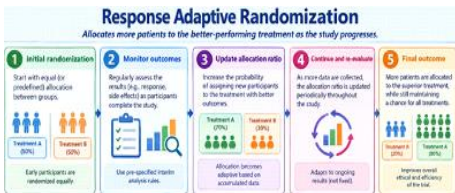


FIG 8: RESPONSE ADAPTIVE RANDOMIZATION

TABLE 1: SELECTION OF AN APPROPRIATE RANDOMIZATION METHOD

Study situation	Potentially appropriate method
Large, parallel two-arm trial	Simple randomization
Need for numerical balance during recruitment	Block randomization
Small trial with important prognostic variables	Stratified randomization
Several interventions evaluated simultaneously	Factorial design
Multiple prognostic variables requiring balance	Covariate-adaptive randomization/minimization
Allocation influenced by accumulating outcome information	Response-adaptive randomization
Intervention delivered to groups or communities	Cluster randomization

No single randomization method is universally superior. The selection should depend on sample size, number of treatment groups, recruitment pattern, number of centres, prognostic factors and whether the intervention is delivered individually or at cluster level.

The selected randomization method should be specified before recruitment begins and incorporated into the trial protocol.

ETHICAL CONSIDERATIONS OF RANDOMIZATION

Randomization raises an important ethical question: should a participant's treatment be determined by chance rather than individual clinical judgement?

The ethical basis for randomization is clinical equipoise, referring to genuine uncertainty regarding which intervention is superior. Randomization is ethically defensible when there is sufficient uncertainty about the

comparative benefits and risks of the interventions being studied. Participants should receive adequate information regarding the purpose of the study, the interventions, potential benefits and risks, the possibility of receiving the comparator or placebo, available alternatives and the right to withdraw.

Randomization should not be used when evidence clearly establishes that one intervention is superior or when allocation would expose participants to unacceptable harm. Clinical trials also involve a balance between individual and collective ethics. Participants may contribute time, effort, travel and undergo additional examinations without a guarantee of personal benefit. Nevertheless, reliable randomized evidence can benefit future patients. Therefore, scientifically inadequate randomization may itself be ethically problematic because participants may be exposed to research burdens without generating reliable knowledge.⁵

ADVANTAGES OF RANDOMIZATION²⁵

1. Reduction of selection bias, 2. Reduction of confounding, 3. Basis for statistical inference, 4. Strengthening causal inference, 5. Protection against investigator preference and 6. Increased credibility. However, randomization cannot eliminate all sources of bias. Problems can still arise from poor allocation concealment, deviations from assigned interventions, loss to follow-up, outcome assessment and selective reporting.

LIMITATIONS²⁵

1. Simple randomization may produce unequal group sizes in small studies.
2. Complex methods such as minimization and response-adaptive randomization require statistical expertise and careful planning.
3. Ethical considerations may prevent randomization when there is strong evidence that one intervention is superior or harmful.
4. Cluster-randomized trials require larger sample sizes and more complex analyses because observations within clusters are correlated.
5. Inadequate reporting of the randomization process can make it difficult for readers and reviewers to determine whether a trial is at risk of selection bias.

CONCLUSION

Randomization is a cornerstone of high-quality clinical trial methodology. Its primary contribution is to prevent predictable treatment allocation and reduce systematic differences between intervention groups, thereby strengthening causal inference. The appropriate randomization strategy should be selected according to the study question, sample size, prognostic factors, recruitment structure and intervention characteristics. Ultimately, randomization is both a statistical and ethical safeguard. A properly designed and transparently reported randomization procedure improves the credibility of clinical research and helps ensure that the risks undertaken by research participants result in scientifically reliable knowledge.

Conflicts of interest: None

REFERENCES

1. Park K. Park's Textbook of Preventive and Social Medicine. 28th edn. Jabalpur: Banarsidas Bhanot Publishers (2025).
2. Schulz, K. F., Altman, D. G. & Moher, D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 340, c332 (2010).
3. Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T. & Page, M. J. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd edn (Wiley, 2019; updated 2024).
4. Sedgwick, P. Allocation concealment. *BMJ* 340, c537 (2010).
5. Coart, E., Bamps, P., Quinaux, E., Sturbois, G., Saad, E. D., Burzykowski, T. & Buyse, M. Minimization in randomized clinical trials. *Stat. Med.* 42, 5285–5311 (2023).
6. Robertson, D. S., Lee, K. M., Lopez-Kolkovska, B. & Villar, S. S. Response-adaptive randomization in clinical trials: from myths to practical

- considerations. *Stat. Sci.* 38, 185–208 (2023).
7. Fisher, R. A. *The Design of Experiments* (Oliver and Boyd, Edinburgh, 1935).
8. Medical Research Council Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 2, 769–782 (1948).
9. Gupta, S. K. *Basic Principles of Clinical Research and Methodology*. 1st edn (Jaypee Brothers Medical Publishers, New Delhi, 2007).
10. Lim, C. Y. & In, J. Randomization in clinical studies. *Korean J. Anesthesiol.* 72, 221–232 (2019).
11. Rosenberger, W. F. & Lachin, J. M. *Randomization in Clinical Trials: Theory and Practice*. 2nd edn (Wiley, Hoboken, 2015).
12. Kernan, W. N., Viscoli, C. M., Makuch, R. W., Brass, L. M. & Horwitz, R. I. Stratified randomization for clinical trials. *J. Clin. Epidemiol.* 52, 19–26 (1999).
13. Suresh, K. P. An overview of randomization techniques: an unbiased assessment of outcome in clinical research. *J. Hum. Reprod. Sci.* 4, 8–11 (2011).
14. Taves, D. R. Minimization: a new method of assigning patients to treatment and control groups. *Clin. Pharmacol. Ther.* 15, 443–453 (1974).
15. Pocock, S. J. & Simon, R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31, 103–115 (1975).
16. Wei, L. J. & Durham, S. The randomized play-the-winner rule in medical trials. *J. Am. Stat. Assoc.* 73, 840–843 (1978).
17. Campbell, M. K., Piaggio, G., Elbourne, D. R. & Altman, D. G. CONSORT 2010 statement: extension to cluster randomised trials. *BMJ* 345, e5661 (2012).
18. Campbell, M. K., Elbourne, D. R. & Altman, D. G. CONSORT statement: extension to cluster randomised trials. *BMJ* 328, 702–708 (2004).
19. Friedman, L. M., Furberg, C. D., DeMets, D. L., Reboussin, D. M. & Granger, C. B. *Fundamentals of Clinical Trials*. 5th edn (Springer, New York, 2015).
20. Donner, A. & Klar, N. *Design and Analysis of Cluster Randomization Trials in Health Research* (Arnold, London, 2000).
21. Eldridge, S. & Kerry, S. *A Practical Guide to Cluster Randomised Trials in Health Services Research* (Wiley, Chichester, 2012).
22. Kim, J. S. & Dailey, R. J. *Biostatistics for Oral Healthcare*. 1st edn (Wiley-Blackwell, Ames, 2007).
23. Alferes, V. R. *Methods of Randomization in Experimental Design*. 2nd edn (Sage, Thousand Oaks, 2012).
24. Robertson, D. S. et al. Response-adaptive randomisation in clinical trials: current practice, gaps and future directions. *Stat. Methods Med. Res.* (2025).
25. Berger, V. W., Bour, L. J., Carter, K., Chipman, J. J., Everett, C. C. & Heussen, N. et al. A roadmap to using randomization in clinical trials. *BMC Med. Res. Methodol.* 21, 168 (2021).