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Techniques for randomization and allocation for clinical trials

Técnicas de randomização e alocação para estudos clínicos

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Abstract

Intervention studies require all participants to originate from the same population, with random allocation to intervention groups to ensure comparability. Randomization is crucial for minimizing confounding factors, allowing differences in outcomes to be attributed to the intervention. Simple randomization performs well for large samples (>100 per group), but smaller samples may require block or stratified randomization to balance group sizes and covariates. When randomization isn't feasible, quasi-randomized methods (e.g., based on dates or enrollment order) can help but must compensate with multivariate adjustments. Moreover, blinding and allocation concealment enhance internal validity and reproducibility. Allocation concealment (e.g., sealed envelopes) prevents bias during participant assignment while blinding mitigates detection and performance biases. Precise methodological descriptions in clinical trial registrations and publications enhance study reliability and reproducibility, highlighting the importance of rigorous planning and transparent reporting in intervention research. This article reviews the key concepts of randomization, blinding, and allocation concealment in interventional studies

Keywords: Randomization; Allocation Concealment; Intervention Studies; Bias Reduction; Methodological Validity.

Resumo

Estudos de intervenção requerem que todos os participantes sejam provenientes da mesma população, com alocação aleatória aos grupos de intervenção (GI) para garantir comparabilidade. A randomização é fundamental para minimizar fatores de confusão, permitindo que diferenças nos resultados sejam atribuídas à intervenção. A randomização simples é eficaz para amostras grandes (>100 por grupo), mas amostras menores podem exigir randomização em blocos ou estratificada para equilibrar os tamanhos dos grupos e as covariáveis. Quando a randomização não é viável, métodos quasi-randomizados (como baseados em datas ou ordem de inclusão) podem ser utilizados, mas devem ser acompanhados de ajustes multivariados. Além disso, o cegamento e a ocultação da alocação aumentam a validade interna e a reprodutibilidade. A ocultação da alocação (ex.: envelopes lacrados) evita vieses durante a designação dos participantes, enquanto o cegamento reduz vieses de detecção e desempenho. Descrições metodológicas detalhadas em registros de ensaios clínicos e publicações aumentam a confiabilidade e a reprodutibilidade dos estudos, destacando a importância de um planejamento rigoroso e de relatórios transparentes em pesquisas de intervenção. Este artigo revisa os principais conceitos de randomização, cegamento e ocultação de alocação em estudos de intervenção.

Palavras-chave: Randomização; Ocultação de Alocação; Estudos de Intervenção; Redução de Viés; Validade Metodológica.

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Quantitative analysis of data collected in intervention studies requires that the sample is drawn from the same population (at each center) and that participants are allocated to groups at random, i.e. with no interference by researchers or participants. This ensures that each individual has the same chance of being designated to any of the intervention groups (IGs).[1-4]

The importance of randomized allocation lies in its capacity to homogenize unknown or unmeasured confounding factors, distributing them across the groups at random. This helps to assemble GIs that are comparable in terms of their baseline characteristics, making attribution of any differences observed to the results of the intervention itself more reliable. To achieve this, in addition to rigorous inclusion criteria, it is imperative to employ techniques for randomization, blinding, and allocation to reduce selection biases and increase the experiment's internal validity, maximizing the reliability and reproducibility of the results.[1,3,5] Some examples of the main types of randomization and their characteristics are given in Chart 1 and 2 respectively.

In its similarity to a simple lottery draw, simple randomization is technically best in terms of comprehensibility and feasibility. However, it can create IGs of disproportionate sizes and can cause imbalances in the proportion of covariates of interest when small samples are used (n < 100). In a study by Coelho et al.,[6] 52 patients were randomized to receive elastic compression therapy for 7 days or to wear elastic stockings for 24 hours after phlebectomy. Demographic covariates were adequately homogeneous, despite a numerical imbalance between the IGs (n = 20 vs. N = 32 participants).

Block randomization guarantees that those allocated are distributed equally among the IGs, avoiding numerical disproportions between different interventions and enabling a certain degree of parallelism in allocations. However, for small samples there is still the risk of imbalance between relevant covariates between IGs. Additionally, in open trials, in which blocks are small, it is possible for researchers to anticipate which intervention will be drawn for the next participant to be allocated to a block, introducing selection bias.[7] In a study by Garcia et al.,[8] 20 participants were randomized in blocks to two IGs, to evaluate two training programs for patients with intermittent claudication. Although the IG sizes were balanced, the sample was too small to enable adequate homogenization of demographic covariates such as sex.

In order to minimize the risk that a covariate of relevance to the study outcome is imbalanced between the IGs and also enable stratified analyses of the results *a posteriori*, stratified block randomization should be used. In practice, this technique creates smaller strata with allocation blocks for individuals with or without the covariates of interest.[7] An example would be stratification of patients with diabetes mellitus or smokers in trials of atherosclerosis treatments.

Randomized block allocation sequences, with or without stratification, can be generated online at sites such as GraphPad[9] and Research Randomizer.[10]

However, even with the stratification of blocks, the use of small samples can still cause inadequate homogenization of potential confounders such as age, sex, or ethnicity within the IGs. These disproportions should then be weighted in the analysis of the results using multivariate analyses. Paired randomization techniques can be used to create more strata or quotas for the inclusion of participants *a priori*. However, balancing the groups for pairing may make it difficult to recruit participants, delaying the study, since paired participants should ideally start their interventions in parallel.[7]

Chart 1. Examples of methods for randomization of 32 participants to two intervention groups (A and B).

Type of randomization	Intervention	Sequence of allocation of the participants
Simple	A	1, 2, 4, 8, 9, 10, 15, 17, 21, 25, 26, 27, 28, 32
	B	3, 5, 6, 7, 11, 12, 13, 14, 16, 18, 19, 20, 22, 23, 24, 29, 30, 31
In blocks	A	1, 3, 6, 8, 9, 12, 14, 16, 17, 20, 21, 24, 26, 28, 29, 31
	B	2, 4, 5, 7, 10, 11, 13, 15, 18, 19, 22, 23, 25, 27, 30, 32
Stratified	A	Stratum X: 1, 3, 6, 8, 9, 12, 14, 16 Stratum Y: 17, 20, 21, 24, 26, 28, 29, 31
	B	Stratum X: 2, 4, 5, 7, 10, 11, 13, 15 Stratum Y: 18, 19, 22, 23, 25, 27, 30, 32
Paired	A	Var W: 1, 3, 6, 8, Var X: 9, 12, 14, 16 Var Y: 17, 20, 21, 24, Var Z: 26, 28, 29, 31
	B	Var W: 2, 4, 5, 7, Var X: 10, 11, 13, 15 Var Y: 18, 19, 22, 23, Var Z: 25, 27, 30, 32
Adaptive by minimization	A	1, 2, 4....dependent on the characteristics of initial recruits for pairing by characteristics.
	B	3, 5, 6
Mendelian	A	1, 2, 4....dependent on the characteristics of the initial recruits for genetic pairing.
	B	3, 5, 6

Chart 2. Advantages and disadvantages of the main methods for randomization in clinical trials.

Randomization method	Advantages	Disadvantages
Simple	Easy to reproduce.	May cause imbalances between groups with small samples.
In blocks	Reduces imbalances between groups.	Allocation sequence can be inferred by researchers in open trials.
Stratified in blocks	Distributes possible predictive factors of the outcome equally across groups.	Generates very small groups when there are many strata, which compromises the power of the statistical analysis.
Paired	Reduces imbalances between groups. Enables comparison of participants with the same predictive factors.	Makes recruitment of patients more difficult, since it should be done simultaneously.
Adaptive by minimization	Enables homogenization between groups to be performed as the study progresses.	Demands continuous monitoring with software.
Mendelian	Enables a constituent factor to be distributed homogeneously between groups.	May be influenced by other exposure factors with other variables that have not been considered (heterogeneous genetics, epigenetics, interaction between genes).

In order not to delay recruitment, adapted randomization by minimization aims to balance the IGs in terms of possible confounding factors, which occur dynamically during the recruitment phase. After initial simple randomization and allocation of some individuals, the baseline characteristics of the groups are analyzed and a calculation is performed to guarantee pairing and balanced stratification of subsequent participants recruited. This method requires software for continuous monitoring during the entire recruitment stage.[11]

In Mendelian randomization, genetic variants associated with the exposure of interest are used as pairing and stratification parameters, which requires prior knowledge of the genetic status of individuals eligible for the study within the population of interest.[12,13]

In general, simple randomization can be used if the sample size is greater than 100 participants per group. When smaller than this, block randomization guarantees better equilibrium of group sizes. However, if there is a need for *a posteriori* analysis by subsets (for example, disease severity, age group, sex/gender, body composition, prior treatments, comorbidities), randomization stratified by the variables of interest should be preferred.[14] More elaborate methods, such as Mendelian, factorial, or cluster randomization, adaptive strategies, and minimization, should be supervised by an experienced statistics professional, with adequate computational support.[15-17]

Researchers should avail themselves of all available resources to guarantee a certain randomization for the allocation of participants to IGs. However, there are situations in which full randomization is not possible. In such cases, the method of non-randomized allocation that stands out is sequential (by convenience), in which participants are allocated based on a sequence defined at the time of recruitment. Quasi-randomized allocation can be used to minimize the burden of lack of randomization, in which a variable, non-random criterion is used to define the GI, such as study registration number (odd or even last number), date of birth, order of recruitment to the clinical trial, or day of the week. Moreover, in retrospective studies that compare interventions (for example, treatment cohorts) and other designs that use non-randomized allocation, conducting sensitivity analyses and multivariate adjustment for confounding variables is essential for ratification of the results.

The entire randomization process is intended to guide the allocation of participants to IGs in a homogeneous manner, according to the study characteristics.[18] It is also important that the allocation process is protected from influence, whether intentional or otherwise, by members of the study research team, in order to minimize inclusion and detection biases. It is also of value to conduct allocation in a manner that precludes researchers from predicting the sequence of interventions, which could introduce bias through the selection of patients more or less favorable for the intervention.[19,20]

Allocation concealment is the term used to describe the randomization process in which the treatment allocated is unknown before the inclusion of the participant in the study.[21,22] This can be achieved using opaque sealed envelopes numbered and organized in advance by someone external to the study team.[23,24]

Blinding, in turn, refers to masking the interventions from the individuals involved in the study after the allocation of participants. It can be applied to the participants (a blind study), to the participant and the investigator or rater of results (double-blind, rater-blind), or to everybody involved (triple-blind).[21] However, it

is not always possible to blind the entire research chain (participants, investigators, and raters) throughout the study and analysis of the results, especially not in surgical trials. In addition to selection bias, detection bias (of outcomes) and performance bias (of the interventions) should be considered in these cases.[25,26] The research team must conscientiously ensure that at least one external rater is blinded to the IGs and that the outcomes are as objective as possible.

There are also exceptional situations that can make randomized allocation difficult since consent to randomization can be difficult to obtain if the patient has a preconceived idea about the interventions involved or when the study involves placebos.[26-29] For ethical reasons, participants may have the right to agree to or refuse the IG allocation to which they are randomized. Trials with special designs (for example, Zelen design, double randomization, crossover trial) were developed to deal with such contingencies and take account of the reallocation of participants after initial randomization, but discussion of these designs is beyond the scope of this text.[30-32]

Finally, regardless of whether intervention studies benefit from techniques for randomization, blinding, and allocation that reduce selection and detection biases, it is still necessary to describe the methodology used in great detail, since this directly affects the internal validity of the results. Whether the methodological description is included on clinical trial registers or provided as supplementary material with the articles, it improves the reproducibility of the study and should be encouraged, even though only a small proportion of clinical trials present such details.[33]

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