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Randomization. Part 1: Sequence generation

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A key feature of a randomized control trial is the process of randomization. Through randomization, we allocate interventions to trial arms in a way that ensures that neither the investigators nor the participants know or can predict ahead of time which treatment a subject will receive. Proper randomization procedures and reporting include the following steps.[1]

1. Generation of the random allocation sequence, including details of any restrictions.
2. Allocation concealment.
3. Implementation of the random allocation sequence: information on who generated the allocation sequence, who enrolled the participants, and who assigned them to their groups.

In this article and the next one, I will discuss popular methods of generating the random allocation sequence. I will explain allocation concealment and implementation of randomization in a separate article.

Many methods for assigning subjects to groups have been used, including sequential treatment assignment, or assignment according to an unrelated factor, such as patient file number, day of the week or month, birthday, or participants' initials. However, these methods are not truly random. They are open to manipulation and have been termed "quasi-randomization" methods.[2]

Popular methods that deliver true randomized allocation include simple, restricted or block, and stratified techniques.

Simple randomization generates randomization lists according to random tables or appropriate software; this resembles the toss of a coin.[2] Random tables include sequences of numbers that occur randomly, with no discernible pattern and with similar frequency, from which we can select numbers in any direction and from any starting point. The Table provides random number sequences from 0 to 9 and can be used as follows: for a 2-arm trial, numbers 0 to 4 can be assigned to treatment A, and numbers 5 to 9 to treatment B. An allocation sequence using this Table and going vertically for 58 patients would be AABBAAAAABBBAAAABBBBBBBBAAAABBBAAAABABA AAABABBAAABAAAABABB (Table columns 1 and 2).

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If we add the As and the Bs, the A:B allocation ratio is 33:25, which is not well balanced between treatment arms. This is often the problem with simple randomization, such as when tossing a coin; when small numbers of patients are recruited, there is a high chance of unequal allocations of participants per treatment arm. As the number to be recruited increases, the imbalances are reduced.

Restricted or block randomization applies constraints to ensure that the trial arms have equal numbers of participants at any time.[2] In block randomization, treatment assignment is done in blocks of a fixed or variable size, which is a multiple of the treatment arms. For a 2-arm trial, the block size might be 4, 6, or 8; in each block, equal numbers for allocation to treatments A and B are included. For example, a block size of 4 might have the following balanced sequences of allocation to treatment A or B: AABB, ABAB, ABBA, BBAA, BABA, or BAAB. Therefore, at the end of each block, there will be equal allocations to A and B.

When a small block size is used—eg, 4—an investigator who knows the first 3 allocations might be able to predict the fourth; to avoid this problem, variable block sizing might be used. For example, block size might randomly vary between 4, 6, and 8, thus making it difficult to predict the next treatment assignment. Allocation prediction is usually a problem in trials where blinding is not feasible, as is often the case in orthodontics. Software is available to generate randomization lists by using random permuted blocks.[3,4]

Stratified randomization is applied to further balance treatment groups in terms of preselected important outcome predictors such as gender, age, center. For example, say that we would like to evaluate the periodontal conditions of orthodontic patients fitted with either conventional or self-ligating appliances in a trial implemented at several locations that serve patients of varying socioeconomic status. One approach would be to create 1 randomization list (either simple or blocked) and allocate treatment centrally, by using the generated list for all trial locations. However, if it were assumed that patients at some locations could have different baseline characteristics that might be important predictors for the outcome (periodontal condition), randomization with a single list could create imbalances of important predictors between the treatment arms. Patients with suboptimal oral hygiene, an important predictor for worse periodontal scores, might

Table. Table of random numbers generated from random.org

1	6	5	0	9	0	5	9	9	0
2	7	9	7	3	3	2	8	4	7
9	2	3	4	3	6	0	9	1	2
6	4	4	4	5	1	1	6	8	5
0	0	3	8	9	0	0	0	3	1
3	0	3	1	1	1	6	4	9	7
1	8	7	9	1	4	2	8	4	0
0	0	7	4	3	2	0	3	6	2
3	5	1	1	4	1	9	8	6	2
7	3	5	3	3	5	7	9	4	9
7	2	4	0	0	1	0	1	6	8
8	1	8	0	5	3	2	7	2	7
2	2	1	0	1	3	7	5	2	9
3	8	0	7	9	6	4	3	6	2
4	3	1	4	9	0	3	7	9	8
4	5	4	6	7	8	7	6	3	7
9	5	3	9	7	4	3	2	7	1
9	2	6	6	9	6	6	7	5	2
6	4	6	1	6	0	1	0	1	2
5	2	7	6	7	8	9	2	6	6
6	6	9	8	4	9	2	7	5	9
8	1	3	7	5	1	8	7	8	1
5	1	6	8	1	4	9	5	1	6
5	2	2	4	0	5	9	6	2	5
1	3	6	6	9	9	0	8	3	0
2	6	4	4	7	2	2	8	8	1
2	1	2	2	9	8	2	3	2	5
3	9	6	0	6	3	5	9	7	7
6	9	7	6	5	5	7	6	8	8

be overrepresented or underrepresented in 1 trial arm, thus confounding (blurring) the trial results. For example, suppose that more patients in wealthy neighborhoods receive conventional brackets and more patients in poorer neighborhoods receive self-ligating brackets. The conventional brackets might seem to be associated with better periodontal health compared with the self-ligating group, since patients in wealthier areas tend to have better oral hygiene habits. In this situation, simple and block randomization will not guarantee balanced treatment groups by location for an important prognostic factor such as oral hygiene. However, balance can be accomplished through stratification (Fig). To ensure balance on important prognostic factors, separate randomization lists might be used for stratification at each location (stratum) and can be combined with blocking to obtain trial arms of equal size within the strata. Stratification can be performed, for example, for sex, or age, or oral hygiene status, or location or for a combination of those factors. However, caution should be exercised not to overstratify on too many factors. For example, if in our example trial

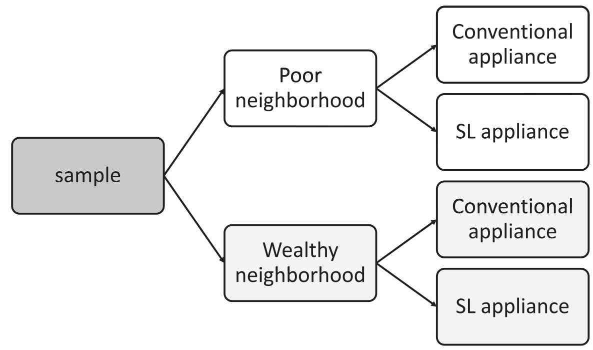

Fig. Stratified randomization to conventional or self-ligating appliances by location. A separate randomization list is generated for each location-neighborhood (stratum).

stratification is performed by sex (2 levels), age ($>$13 and $<$13 years), oral hygiene status (bad, good, excellent), and center (3 locations), the number of strata introduced would be $2 \times 2 \times 3 \times 3 = 36$. Having many strata creates several small subgroups and treatment allocation imbalances by potentially forming several incomplete blocks. If several prognostic factors are considered, perhaps the generation of an index and stratification on the index will be prudent; alternatively, the method of minimization can be used.

Another issue with stratification is related to the fact that, ideally, all participants should be identified before randomization, but this is often difficult for a trial that recruits prospectively. Finally, stratification is more important for trials with small sample sizes where imbalances of important prognostic predictors are more likely.

The next article in the series will discuss the method of minimization.

KEY POINTS

- Simple randomization is likely to create imbalances especially, in small trials.
- Restricted randomization ensures balance at all stages of recruiting.
- Stratified randomization ensures balance in important prognostic factors and is especially important in small trials.

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