JAMA Guide to Statistics and Methods

Randomization in Clinical Trials
Permuted Blocks and Stratification

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The most compelling way to establish that an intervention definitively causes a clinical outcome is to randomly allocate patients into treatment groups. Randomization helps to ensure that a certain proportion of patients receive each treatment and that the treatment groups being compared are similar in both measured and unmeasured patient characteristics.[1,2] Simple or unrestricted, equal randomization of patients between 2 treatment groups is equivalent to tossing a fair coin for each patient assignment.[2,3] As the sample size increases, the 2 groups will become more perfectly balanced. However, this balance is not guaranteed when there are relatively few patients enrolled in a trial. In the coin toss scenario, obtaining several consecutive heads, for example, is more likely than typically perceived.[1,4] If a long series of assignments to 1 group occurred when randomizing patients in a clinical trial, imbalances between the groups would occur.

Imbalances between groups can be minimized in small sample–size studies by restricting the randomization procedure. Restricted randomization means that simple randomization is applied within defined groups of patients. Two recent articles in *JAMA* used restrictions on the randomization procedure: Bilecen et al[5] used permuted block randomization, a restricted randomization method used to help ensure the balance of the number of patients assigned to each treatment group.[3] Kim et al[6] used a stratified randomization scheme together with permuted block randomization. Stratified randomization is a restricted randomization method used to balance one or a few prespecified prognostic characteristics between treatment groups.[1]

Explanation of the Concept

What Are Permuted Blocks and Stratified Randomization?

The permuted block technique randomizes patients between groups within a set of study participants, called a block. Treatment assignments within blocks are determined so that they are random in order but that the desired allocation proportions are achieved exactly within each block. In a 2-group trial with equal allocation and a block size of 6, 3 patients in each block would be assigned to the control and 3 to the treatment and the ordering of those 6 assignments would be random. For example, with treatment labels A and B, possible blocks might be: ABBABA, BABBAA, and AABABB. As each block is filled, the trial is guaranteed to have the desired allocation to each group.

Stratified randomization requires identification of key prognostic characteristics that are measurable at the time of randomization and are considered to be strongly associated with the primary outcome. The categories of the prognostic characteristics define the strata and the total number of strata for randomization is the product of the number of categories across the selected prognostic characteristics.[1,7] Randomization is then performed separately within each stratum.[7] For example if randomization were stratified by sex (men vs women) and age (<40, 40-59, ≥60 years), there would be a total of 6 strata. Randomization within each stratum could be a simple randomization or could be a permuted block randomization.

Why Are Permuted Blocks and Stratified Randomization Important?

The most efficient allocation of patients for maximizing statistical power is often equal allocation into groups. Power to detect a treatment effect is increased as the standard error of the treatment-effect estimate is decreased. In a 2-group setting, allocating more patients to 1 group would reduce the standard error for that 1 group but doing so would decrease the sample size and increase the standard error in the other group. The standard error of the treatment effect or the difference between the groups is therefore minimized with equal allocation.[8] Permuted block randomization avoids such imbalances.[2] This is an important consideration for trials with planned interim analyses because interim analyses may be conducted using small sample sizes resulting in a greater chance of having large imbalances in the allocation of patients between groups.[1,4,7]

Stratified randomization ensures balance between treatment groups for the selected, measurable prognostic characteristics used to define the strata. Because stratified randomization essentially produces a randomized trial within each stratum, stratification can be used when different patient populations are being enrolled or if it is important to analyze results within the subgroups defined by the stratifying characteristics.[3,7] For example, when there are concerns that an intervention is influenced by patient sex, stratification might occur by sex. Because patients are randomly allocated both in the male and female groups, the effect of the intervention can be tested for the entire population and—assuming sufficient sample size—separately in men and women.

Limitations of Permuted Block Randomization and Stratified Randomization

The main limitation of permuted block randomization is the potential for bias if treatment assignments become known or predictable.[1,9] For example, with a block size of 4, if an investigator knew the first 3 assignments in the block, the investigator also would know with certainty the assignment for the next patient enrolled. The use of reasonably large block sizes, random block sizes, and strong blinding procedures such as double-blind treatment assignments and identical-appearing placebos are strategies used to prevent this.

In stratified randomization, the number of strata should be fairly limited, such as 3 or 4, but even fewer strata should be used in trials enrolling relatively few research participants.[7,10] There is no particular statistical disadvantage to stratification, but strata do result in more complex randomization procedures.[3] In some settings, stratified randomization may not be possible because it is simply not feasible to determine a patient's prognostic characteristics before getting a treatment assignment, such as in an emergency setting. An alternative to stratification is to prespecify a statistical adjustment for the key characteristics in the primary analysis that are thought to influence outcomes and may not be completely balanced between groups by the randomization procedure. Another alternative to stratification is minimization.[7] Minimization considers the current balance of the key prognostic characteristics between treatment groups and if an imbalance exists, assigns future patients as necessary to rebalance the groups.[7] For example, if the experimental group had a smaller proportion of women than did the control group and the next patient to be randomized is a woman, a minimization procedure might assign that patient to the experimental group. Minimization can be more complex than stratification, but is effective and can accommodate more factors than stratification.[7]

How Were These Approaches to Randomization Used?

Bilecen et al[5] reported a single-center randomized clinical trial comparing a fibrinogen concentrate with placebo in reducing intraoperative bleeding during high-risk cardiac surgery, with a total sample size of 120 patients. In this study, patients were randomized according to a permuted block randomization scheme with a block size of 4. With this randomization scheme, the entire randomization list can be generated before a single patient is enrolled. Random treatment assignments are generated in groups of 4, by randomly selecting 2 of the assignments to be to the control group and then allowing the remaining 2 assignments to be to the treatment group. As each patient is randomized into the trial, the patient receives the next sequential assignment on the randomization list. The study by Bilecen et al had an equal number of patients randomized into the 2 treatment groups. The block sizes were small, so randomization was performed centrally and blinding procedures were in place to minimize the ability of the investigators to predict the randomization sequence.

Kim et al[6] performed a multicenter clinical trial assessing the hemoglobin response at 12 weeks among patients undergoing radical gastrectomy after administration of ferric carboxymaltose or placebo. A total of 454 patients were randomized using both stratification and permuted blocks with random block sizes. Randomization was stratified at each site based on the clinical stage of gastric cancer. For this randomization scheme, a randomization list can be generated prior to the start of the trial as well, but 1 randomization list must be generated for each site and clinical stage strata. A sequence of block sizes is randomly generated where allowable block sizes were 2, 4, or 6 in this study. Within each block, half of the assignments are randomly selected to be to the control group and remaining assignments are allowed to be to the treatment group. As each patient is randomized into the trial, the patient receives the next sequential assignment on the randomization list specific to his/her site and clinical cancer stage. The use of a random block size ensures that the next randomization assignment cannot be guessed. Because this was a multicenter trial with 7 sites, randomization within each site ensures that a site discontinuing participation in the trial or enrolling poorly would not affect the overall balance of the treatment groups.[2,7] Stratifying by clinical cancer stage ensures that the control and intervention groups are balanced on this 1 important prognostic characteristic. The treatment groups were nearly equal in size and were balanced for cancer stage. While Kim et al did not report the primary efficacy results by cancer stage subgroups, it would have been appropriate to do so.

How Does the Approach to Randomization Affect the Trial's Interpretation?

In a clinical trial, the ultimate goal of the randomization procedure is to create similar treatment groups that allow an unbiased comparison. Restricted randomization procedures such as stratified randomization and permuted block randomization create balance between important prognostic characteristics and are useful when conducting randomized trials enrolling relatively few patients.[3] In the cases of the trials by Bilecen et al and by Kim et al, the restricted randomization procedures minimized the risk of biased study results by ensuring balanced treatment groups.

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