Chapter 15
Methods and Timing of Randomization

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Reasons to Conduct Randomized Trials

In randomized control trials comparing a control group and an intervention group, each trial participant has the same chance (most often 1 to 1) of being assigned to the respective groups. Some trials, especially Phase I or II drug trials, have uneven assignment such as two for intervention to every one for control to collect more information on participants' response to the intervention. It is important to consider what type of blinding will be used in the trial, either single blind (where the participant does not know the assignment, to eliminate subjective bias or the "placebo effect," but the physician does) or double blind (where neither knows the assignment). Drug trials usually are double blind, while invasive trials often use single blind since it is difficult if not impossible to blind the treating physician.

The randomized design for choosing controls has several advantages over other options [1].

1. Use of a randomization procedure under which the assignment to group cannot be anticipated avoids the potential for bias in making group assignments.
2. Randomization tends to balance the groups on important prognostic factors and participant characteristics, even on variables which are unknown and unmeasured.
3. Randomization assures the validity of statistical tests of significance, by allowing the assignment of a probability distribution to the difference in outcome between groups receiving equally effective treatments.

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Randomization Procedures

Prior to randomization, the potential study participant must be identified by the study staff, provide informed consent, meet the eligibility criteria, and agree to be randomized [2]. There are numerous methods for performing randomization; the description below follows Chap. 6 of [3].

With a *fixed allocation randomization* procedure, the probability of being assigned to the intervention or control is the same for each participant throughout the study. Fixed allocation procedures include the following.

1. Simple randomization, which uses a fair process (e.g., use of an unbiased coin or random number generator) to make assignments.
2. Blocked randomization, where assignments are made for multiple participants based on blocks with an equal number of assignments for each group (e.g., if there are two groups A and B, a block of size 4 would be any of the six possible orderings with two A's and two B's). Two refinements of blocked randomization may be implemented to reduce the likelihood of knowing the treatment assignment pattern. The first is permuted block randomization, in which the randomization sequence varies from one block to the next. The second is permuted block randomization with random block sizes, which employs a second level of randomization to randomly determine the size of the next permuted block.
3. Stratified randomization, under which the assignment is done independently within each combination of levels for characteristics deemed to be correlated with the primary study outcome. For example, if you want to stratify on sex, and age <60 or not, you would have 2*2 or 4 strata. Stratified randomization can be applied to simple or blocked (and permuted block) randomization.
4. For these randomization methods, the randomization codes for the study can be determined prior to starting recruitment using a computer program. The code list should be created and maintained by someone not involved in recruitment or follow-up of study participants.

Under an *adaptive randomization* procedure, the probability of assignment to group changes as the study proceeds. Some adaptive randomization procedures are described below.

1. Baseline adaptive randomization, where the goal is to balance the number of participants in each group. There are common techniques for performing baseline adaptive randomization, described below; however, these are less frequently used in randomized clinical trials.

   (a) The biased coin method [4] is based on assignments made for already randomized participants when making the assignment for the next participant but it does not consider the participants' responses. If the counts by group are equal or nearly so, then the next assignment is made with equal probability. If the count imbalance is greater than a pre-specified amount, the group with the lower count has a better than equal chance of being assigned.

(b) The urn design [5–8] refers to randomly selecting a ball from an urn filled with balls of different colors with each color representing a treatment group. Say red balls are for Group A and black balls are for Group B. For the first assignment there are an equal number of balls by color. If the first ball selected is red, that participant is assigned to Group A, and the red ball is returned to the urn and one or more black balls are added. If the first selection is a black ball, the participant is assigned to Group B and the black ball is returned to the urn and one or more red balls are added. Repeat this process for each assignment.

2. The minimization method [9] strives to balance overall assignments between groups for a set of baseline characteristics. This method is often employed when the number of combinations of baseline characteristics is large relative to the planned sample size for the study, which makes stratified randomization impractical. However, this method requires a computer program to be run for each randomization. For the example described above for stratified randomization, minimization would tend to balance counts by group for males (regardless of age category or enrolling site), females, age <60, and age ≥ 60. The assignment for the next participant is based on the counts by group of similar participants already randomized. Say for the example above the study already has ten participants randomized and the counts by group and stratification factor are given in Table 15.1. If the next participant is female and 58 years old, tallying by group the numbers in the female and <60 rows results in a count of 1 + 3 = 4 for Group A and 2 + 4 = 6 for Group B. Since the count is smaller for Group A, the assignment for the eleventh randomization is Group A.
3. Response adaptive randomization considers the participants' responses to the study treatment when making the assignment for the next participant. Common models for response adaptive randomization are described below, each of which assumes there are one or two treatment groups, and the participants' response to treatment can be ascertained quickly relative to the length of the study.

(a) Under the play-the-winner model [10], after the first assignment, the second participant receives the same assignment if the first participant's response

Table 15.1 Randomization counts by group and stratification factor in example

		Number randomized by group		
Stratification factor	Level	A	B	Characteristics of next participant
Sex	Male	4	3	
	Female	1	2	X
Age	<60	3	4	X
	≥ 60	2	1	

was successful; otherwise, the second participant is assigned to the other group. The process continues where the next assignment is based on the successful or unsuccessful response of the immediately preceding participant.

(b) For the two-armed bandit model [11], the probability of success is updated as soon as the response is known for each participant, and group assignment probabilities are adjusted so that the treatment currently deemed "better" would be assigned to a higher proportion of future participants.

For the randomization methods cited above, Table 15.2 summarizes the advantages and disadvantages and provides recommendations on when the method should be used in a given study.

Mechanism and Timing of Randomization

Whichever randomization method is used, it should be implemented in the proper manner (e.g., to avoid revealing treatment assignment to blinded participants or site staff). It is common to have an independent entity (e.g., a data coordinating center or a biostatistician or clinician not involved in participant care) be responsible for developing the randomization procedures and making treatment assignments. The enrolling site staff may contact the independent entity or use a study website to get the assignment, and part of the process should be to have site staff verify that the participant meets eligibility criteria before receiving the group assignment.

It is important to have randomization performed as closely as possible to the time when the participant is deemed eligible and ready to begin treatment; if randomized before this, the participant may decide to withdraw, the participant's medical condition may change so they no longer meet the eligibility criteria, or the physician may feel the participant is no longer a good study candidate before the participant starts treatment. The withdrawal of participants between the time of randomization and start of therapy may lead to biased study results unless the analysis follows the intent-to-treat principle and includes data for all randomized participants [12].

Even when randomization is well timed with the start of treatment, problems may occur. For example, say the results of an invasive procedure are needed to determine whether the participant is eligible, and the process is to obtain the randomized assignment while the participant is on the operating table, and then perform the assigned treatment. The interruption of the operative procedure to get the treatment assignment may be disruptive, especially if it takes a while to get the assignment or if the randomization system is not available. The physician must always put the highest priority on the patient's safety and welfare, even if that means not randomizing that participant.

Table 15.2 Advantages, disadvantages, and usage recommendations for various randomization methods

Method	Advantages	Disadvantages	Usage recommendations
Simple	1. Simple to perform 2. Each assignment cannot be predicted	1. May lead to large relative imbalance, especially if sample size is small	1. Not used often 2. Only consider if sample size is over 200 [2]
Blocked	1. Avoids serious group imbalance and ensures imbalance is never large and at times there is no imbalance	1. If block size does not vary and is known, last assignment in each block known 2. Data analysis more complicated than Simple	1. Use if study has more than several hundred participants 2. Often used in combination with Stratified 3. If blocked and stratified, include baseline variables used to determine assignments as covariates in analyses
Stratified	1. Ensures group balance in prognostic factors 2. Power of study is increased if stratification is accounted for in the analysis	1. Must decide which prognostic factors will influence treatment response 2. Must be able to easily and reliably obtain participant's status on stratification factors	1. Use when prognostic factors are so important that you do not want to risk randomization producing imbalanced groups 2. More useful for small studies since large samples increase chance of groups having similar characteristics 3. Control number of stratification factors to avoid small number of participants in any given stratum. Often some factors considered are highly correlated so many may be dropped without affecting the balance of assignments by group 4. Enrolling sites may have important differences (e.g., patient characteristics, methods and quality of treatment, available equipment, degree to which they follow the protocol) [12], so consider having site as a stratification factor

(continued)

Table 15.2 (continued)

Method	Advantages	Disadvantages	Usage recommendations
Baseline adaptive	1. Less susceptible than blocked to selection bias	1. Blocked controls group balance more closely 2. More complicated than Simple, Blocked, Stratified 3. Population needs to be stable throughout study enrollment (e.g., if entry criteria changed, adaptive methods may not be able to fix imbalance existing before change)	1. Often used in conjunction with stratified
Minimization	1. Better balance than Blocked and Stratified when there are lots of prognostic factors and a small sample 2. Provides unbiased estimates of treatment effect and slightly increased power compared to Stratified [13]	1. More complicated than Simple, Blocked, Stratified 2. Population needs to be stable throughout study enrollment 3. Only time assignment determined randomly is when group counts are the same	1. Include baseline variables used to determine assignments as covariates in analyses [14, 15]
Response adaptive	1. Maximizes proportion of participants on "better" treatment	1. Limited to studies with one or two groups 2. Primary response variable must be measurable quickly relative to study length 3. May have several important response variables so it is difficult to choose the most important 4. Population needs to be stable throughout study enrollment 5. Possible imbalance likely to result in loss of power and larger sample size than fixed allocation randomization with equal assignment probabilities [16]	1. Procedures are complicated, so not often used

Mechanics of Randomization

There are various ways to inform the recruiting site of the participant's treatment assignment (for an unblinded or single-blind trial) or coded assignment (for a double-blind study), including the following.

1. Transferring the randomization list to a series of cards in sealed envelopes with envelopes numbered sequentially to follow the order of the list and instructing the site staff to open the next envelope in series with the next participant are ready to be randomized. Pocock [2] suggests using this method only if randomization is not done centrally and there is no one else for the site to consult with for randomization. Also, this method is not compatible with the adaptive randomization procedures described above.
2. Having the site contact (via telephone, email, etc.) a staff member at the centralized office who goes through the process to produce the randomization assignment and communicate it to the site staff. One drawback of this option is randomization may only occur when the centralized office is staffed.
3. Having the site staff contact a voice response system connected to a computer which takes the place of the centralized office in Option 2 above. With this method, sites may randomize at any time as long as the voice response system and computer are functioning properly.
4. Having the site staff use a web-based system in a manner similar to Option 3 above.

Since none of these options are totally reliable, it is a good idea to have one or more backup randomization methods in place for the study. For example, your primary method could be web-based with the option to call or email the centralized randomization staff if the website is down or otherwise unavailable to the site staff.

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