Research Series

# Eliminating Bias in Randomized Controlled Trials: Importance of Allocation Concealment and Masking

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*Randomization in randomized controlled trials involves more than generation of a random sequence by which to assign subjects. For randomization to be successfully implemented, the randomization sequence must be adequately protected (concealed) so that investigators, involved health care providers, and subjects are not aware of the upcoming assignment. The absence of adequate allocation concealment can lead to selection bias, one of the very problems that randomization was supposed to eliminate. Authors of reports of randomized trials should provide enough details on how allocation concealment was achieved so the reader can determine the likelihood of success. Fortunately, a plan of allocation concealment can always be incorporated into the design of a randomized trial. Certain methods minimize the risk of concealment failing more than others. Keeping knowledge of subjects' assignment after allocation from subjects, investigators/health care providers, or those assessing outcomes is referred to as masking (also known as blinding). The goal of masking is to prevent ascertainment bias. In contrast to allocation concealment, masking cannot always be incorporated into a randomized controlled trial. Both allocation concealment and masking add to the elimination of bias in randomized controlled trials.*

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The randomized controlled trial (RCT) is considered the strongest research design for evaluating the effects of health interventions.[1] A number of articles and textbooks provide readers of clinical trials with a list of criteria with which to assess their validity.[2-4] The Consolidated Statement of Reporting Trials (CONSORT), published in three major journals in 2001, aims to improve the reporting of clinical trials so that readers can assess validity based on standard criteria.[1,5,6] Two such criteria are whether the trial used a method to generate a random allocation sequence (what is often simply called "randomization") and whether allocation was concealed.

Authors will usually point out (or claim) that they have met the "randomization" criterion in the title of the article. However, randomization (sequence generation) schemes differ, and some schemes claim to be randomized when they really are not.[7] For example, systematic selection schemes, such as recruiting subjects who present to clinic on certain days, are not randomized. Even assigning subjects based on something seemingly random such as first letter of the last name may not be random, since some ethnic groups would end up being disproportionately assigned.

Even less well understood, and often more difficult to ascertain, is whether allocation was concealed. Allocation concealment is actually part of the randomization process, and while distinct from the method used to generate the randomized sequence, is crucial to the success of randomization. A third standard criterion used in judging validity of an RCT—one that may be confused with allocation concealment but is distinctly different—is masking.

## Randomization and Masking

Randomization is best thought of as a series of events that includes, but is not limited to, the generation of a random allocation sequence. While the process of randomization begins with this sequence generation process, it does not end until subjects are actually assigned to their groups (eg, intervention or control). The processes of allocation concealment and actual implementation of assignments must follow the sequence generation.

Masking (blinding) in a clinical trial refers to a process that attempts to keep the group (eg, active

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drug or placebo) to which the study subjects are assigned not known or easily ascertained by those who are "masked." Masking can occur at the level of the subjects, investigators, health care providers, data collectors, and those assessing outcomes (Figure 1).

Many readers will be familiar with the term "double-blind" as used with RCTs and assume that this term means that the study subjects and the health care providers were unaware as to which group subjects were allocated. However, the term double-blind does not have a standard definition and cannot always be relied upon to convey which groups in a randomized controlled trial were masked.[8] It might be understood to mean that study subjects and investigators, or study subjects and outcome assessors, or health care providers and investigators, or any combination of groups involved, were unaware of group assignment. Likewise, the terms "single-blind" and "triple-blind" do not have standard definitions. Because of the ambiguity of these terms, descriptions of masking in reports of RCTs ideally should be explicit, describing precisely who was masked.[8]

## Why Are Randomization and Masking Important?

*Randomization Adds Validity to Statistical Tests*

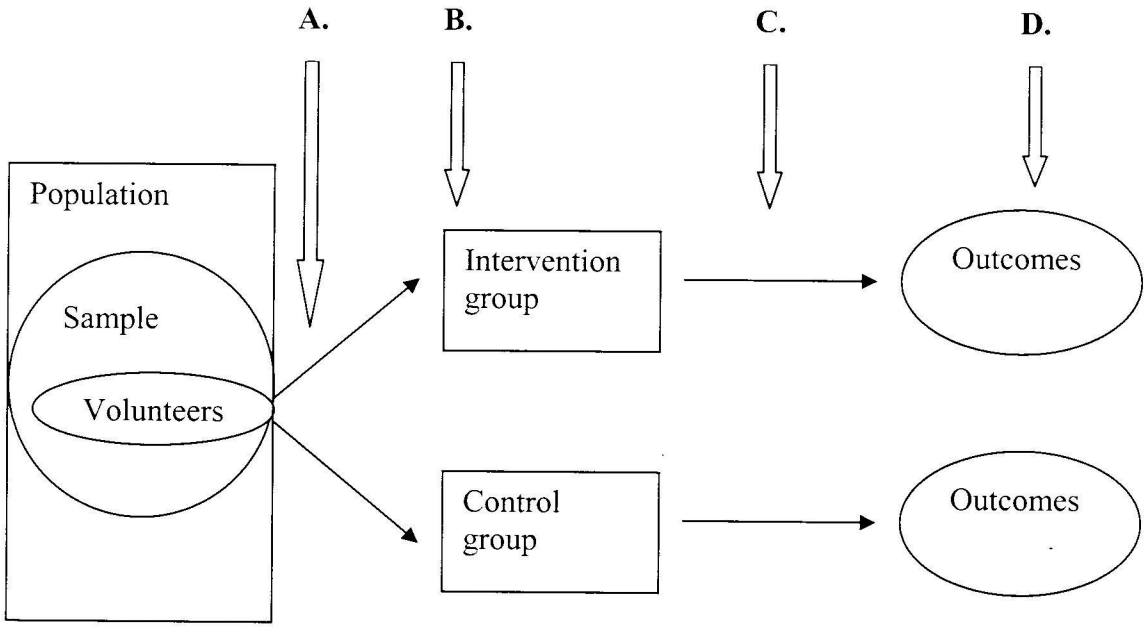
The first strength of the RCT is that randomization adds to the validity of the statistical tests used to demonstrate significance.[7] That is, because differences between intervention and control groups should behave like differences between two random samples from the population, they can be compared to what would be expected in the population by chance.[7] Of course, statistical tests also rest on other assumptions (eg, normal variance distributions, sufficient sample size) that are independent of whether randomization was part of the research design.

*Randomization Minimizes Confounding*

The second strength of the RCT also stems from proper randomization. Randomization tends to produce groups that are similar in terms of both known and unknown prognostic factors.[7] By generating two groups of subjects with similar characteristics, the randomization minimizes confounding—the bias that occurs when

Figure 1

General Design of a Randomized Controlled Trial




A. Randomization and allocation concealment
B. Actual assignment that can be followed by masking subjects as to their assigned group
C. Prospective evaluation period during which health care providers, investigators, and/or external monitoring committees (eg, data safety monitoring board) can be masked as to the subjects' assigned group
D. Outcome evaluation or adjudication during which outcome asessors can be masked as to the subjects' assigned group

one group of subjects has certain features (known or unknown) that affect the relationship between the intervention and the outcome of interest.

Readers of RCTs will often see the comparison of the groups in a table showing key baseline characteristics of study participants by treatment arm, often "Table 1" in a published report. The readers (keeping in mind that trials with fewer participants are more likely to have between-group differences of a clinically important magnitude by chance) can then judge for themselves whether randomization was successful or whether there was a possibility of sampling error. If there are differences in important factors at baseline, one should consider the magnitude of any chance differences and how strongly they may affect the outcome. Lastly, using the baseline characteristics table, readers can consider if the population is similar enough to their patient population to make the results generalizable.

*Masking Reduces Remaining Biases*

An RCT is additionally strengthened by including masking when possible. The goal of masking is to eliminate, or at least minimize, remaining potential biases.[9] Refer again to Figure 1 and note that bias can occur at several points in a clinical trial. For example, at point C during the trial, knowledge of group assignment by health care providers might influence clinical care of subjects. However, not knowing to which group a subject has been assigned, health care providers and/or investigators theoretically would not influence the outcome of one group any more than the other. A data safety and monitoring board (DSMB) can be masked at this point as well, but this does not occur that frequently.

At point D, unmasked outcome assessors—such as a committee charged with making a final determination based on clinical judgment as to whether each subject achieved a study endpoint—may be biased in their assessments based on preconceived notions of "expected" outcomes. Masking of study personnel assessing outcomes strengthens their objectivity, especially when the outcome is not a hard outcome (eg, death).

Subjects who are unmasked (point B in Figure 1) are more likely to alter their behavior or their self-assessment of key study endpoints (such as quality of life) if they know their assignment. Masked subjects are more likely to adhere to their assigned treatment. That is, when subjects do not know to which group they were assigned, they are less likely to cross over from control group (eg, placebo) to study intervention group (eg, active drug) or vice versa. Also, masked subjects are less likely to drop out of the study entirely.

*Ethical Aspects*

In addition to minimizing biases, masking and randomization have ethical aspects. By masking after assignment, the groups should be treated equally on all other accounts except the intervention under investigation. By proper randomization in assigning subjects to the intervention or control group, there is no dependence on good intentions. As mentioned earlier, however, successful implementation of randomization is dependent on allocation concealment.

**Allocation Concealment**

Simply put, allocation concealment refers to preventing the next assignment in the clinical trial from being known (point A in Figure 1). In other words, a system must be in place to ensure that subjects, investigators, and involved health care providers do not know to which group a subject will be allocated before that subject is entered into the study. If the next group to which a subject will be allocated is known, either by there being no effort to conceal it or by deciphering the randomization scheme, the RCT potentially becomes a nonrandomized trial.

Let us imagine that Dr PI is conducting a randomized controlled trial to study whether a new drug called Slimmenow helps patients lose weight. Subjects meeting eligibility criteria will be referred to study personnel from their participating health care providers. This study is well funded, and each participant will be provided nutritional consultations and a personal trainer. Subjects will be randomized to either Slimmenow or a placebo pill that looks, smells, and tastes like Slimmenow.

If the referring health care provider is aware of the next allocation, he/she may (even unknowingly) influence enrollment or selection of participating subjects. For example, if the referring health care provider knows the next subject will be allocated to Slimmenow, he/she may be inclined to try to help a certain patient he/she thinks may benefit more. Or perhaps knowing the next subject is to be allocated to placebo, he/she refers someone who really does not need to lose much weight. Whatever referral pattern occurs as a result of the referring health care provider's knowledge of allocation will introduce selection bias that the randomization was designed to eliminate. Knowledge of allocation by the trial investigator(s) can affect the trial similarly.

Subjects are probably hoping to be randomized to Slimmenow. It is possible that a subject could become aware of an upcoming treatment assignment, for example, if envelopes are opened too early or if an allocation list is posted. If a subject becomes aware of the allocation scheme prior to enrollment, knowledge of allocation to placebo might cause the subject to refuse to participate entirely. Alternatively, the subject may wait until the allocation is to the active drug before enrolling. Again, the results are loss of randomization and introduction of bias.

Without allocation concealment, the effects of the intervention tend to be overestimated. In fact, trials

with inadequate allocation concealment yield estimates of treatment effect up to 40% larger than trials using adequate allocation concealment.[10,11] Therefore, a large treatment effect from a "randomized" trial without adequate allocation concealment might simply reflect biased allocation. However, because such biases are supposedly minimized in RCTs as compared to observational studies, authors may not point out such potential biases in their published paper. Readers must therefore be more alert to such possibilities.

In a relatively recent trial of glucosamine for chronic knee pain, 46 adults were purportedly randomized to either glucosamine (n=24) or placebo (n=22).[12] The only information provided to the reader regarding randomization is that "A double-blind experimental design was employed, and subjects were randomly assigned to either the placebo (P) or glucosamine (G) group based on the order in which they attended their first assessment session." After 12 weeks, 88% of those in the glucosamine group compared to 17% in the placebo group reported improvement in their knee pain. If allocation concealment was inadequate, some subjects (perhaps those with pain of longer duration) could have been "selected" to the placebo group. The effect would be an overestimation of the effect of glucosamine.

While inadequate allocation concealment tends to produce exaggerated treatment effects, it is also possible that a biased allocation resulting from inadequate concealment might lead to underestimation of the effect of an intervention. In the example above, if subjects with pain of longer duration or more severe pain were 'selected' to the glucosamine group, the effect of glucosamine might be underestimated. Again, the direction of fluctuation would depend on whatever pattern emerged as a result of non-concealed allocation.

**Preventing Deciphering**

Trial designers must make every effort to ensure that allocation concealment schemes do not become known. Deciphering does occur, most commonly because the method of allocation concealment was inadequate.[13] Personal accounts of deciphering and subverting allocation schemes have been documented.[13] Indeed, even the best allocation concealment schemes have been circumvented by various methods (Table 1).[10,13] It seems that deciphering the "secret code" is too great a temptation to some people involved in trials, and many may be naïve as to the consequences for the scientific integrity of the trial.[10] Once the upcoming assignment becomes known, enrollment or allocation to particular study groups can be altered, and the randomized trial has been sabotaged.

Reports of allocation concealment should include a description of the method used with enough detail for the reader to determine the likelihood of undermining the process. The randomization and masking items from the CONSORT checklist are shown in Table 2.[1,5,6] Schulz and Grimes have described minimum and expanded criteria by which the reader can be assured of adequate allocation concealment (Table 3).[10]

Returning to our example of a randomized controlled trial of Slimmenow versus placebo, let us imagine we read in the published report of the trial that assignment to intervention or control group was made by having the referring health care provider draw an envelope from a large box of sealed envelopes; each contain a letter designating the next allocation (eg, "A" for intervention, "B" for control). If that is the sole description of the method of allocation, we cannot be certain that allocation was concealed. A referring health care provider may have held envelopes to a bright light to learn the next allocation. Alternatively, envelopes may have been opened prior to assigning the subject.

A more-reassuring description of allocation concealment may have read: "Assignment was made by sequentially numbered, otherwise identical, sealed envelopes, each containing a 2-inch by 2-inch paper with a written code designating intervention or control. These papers were placed in a folded sheet of aluminum foil fitted inside the envelope. There were no detectable differences in size or weight between intervention and control envelopes. Envelopes were opaque and lined inside with carbon paper. Envelopes were opened sequentially only after writing the subject's tracking information on the envelope so that the carbon paper served as an audit trail."

The use of sequentially numbered, opaque, sealed envelopes (SNOSE) is an economical and straightforward means of assuring allocation concealment. It works as well as other methods that might require specialized technology.[14,15] Of course, the additional precautions (ie, aluminum foil, carbon paper) may not be necessary, but one can appreciate the added difficulty in unmasking this sort of allocation scheme.

The important point is that when using envelopes to

Table 1

Examples of Methods of Deciphering Allocation Concealment[10]

- Holding translucent envelopes up to bright lights to reveal upcoming assignment (even using the hot light in a radiology department for more opaque envelopes)
- Opening unsealed assignment envelopes
- Opening a well-sealed, opaque envelope in advance of consent
- Opening unnumbered envelopes until desired allocation found
- Determining different weights of the assignment envelopes (eg, the heavier envelope means intervention group)
- Asking a central randomization center for the next several assignments all at once
- Deciphering assignments to active drug or placebo based on appearance of drug container labels

Table 2

CONSORT Checklist of Items Pertaining to Randomization and Masking When Reporting a Randomized Trial[1,5,6]

| *Section and Topic* | *Descriptor* |
|---|---|
| Randomization | |
| • Sequence generation | Method used to generate the random allocation sequence, including any details of any restriction (eg, blocking, stratification). |
| • Allocation concealment | Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until the interventions were assigned. |
| • Implementation | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups? |
| Blinding (masking) | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. |

CONSORT—Consolidated Statement of Reporting Trials

Table 3

Suggested Minimum and Expanded Descriptions of Allocation Concealment[10]

| *Examples of Minimum Description of Adequate Allocation Concealment* | *Expanded Descriptions Providing Greater Assurance of Allocation Concealment* |
|---|---|
| Central randomization | Mechanism for contact is described (eg, telephone, e-mail, fax). Precautions taken to ensure enrollment prior to allocation as well as description of training for individuals staffing the central office are provided. |
| Pharmacy controlled | Description provides indications that the researchers developed or validated a proper randomization scheme for use by the pharmacy. Description that the pharmacy was provided instruction in allocation concealment. |
| Sequentially numbered containers | Description provides details of no detectable differences between containers. Containers were equal in weight, similar in appearance, and tamper-proof. |
| Sequentially numbered, opaque, sealed envelopes ("SNOSE") | Description of details on how tampering and discovery was prevented (eg, carbon paper lined to create an audit trail, aluminum foil or cardboard placed inside to prevent "hot lighting"). |

Adapted from: Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet.* Feb 16 2002;359(9306):614-618.

make allocation assignments, there should be a mechanism to provide a trail to document that an envelope was not opened prior to consent, because envelope-based allocation may be the most susceptible to deciphering. Alternatively, use of a modern centralized or remote telephone-based, computer-based, or Web-based allocation system should be considered when possible. Computerized time stamps and electronic logs can serve as methods to monitor allocation concealment with such systems, further minimizing the risk of allocation concealment failing.

Allocation concealment may also be violated if the study investigators can correctly guess the next assignment. Investigators will generally want to closely balance the number of subjects allocated to study arms at any given time during the recruitment phase. Randomization is not done by coin flips at each point because investigators need to assure approximate balance between group assignments at all points in the study. Such balance is helpful for maximizing power of any interim analyses (eg, analyses performed for a DSMB).

Because subjects in studies are not recruited all at once, randomization is often done in smaller blocks of subjects. When randomization is performed in blocks, the number of subjects allocated within a block is the same for all study arms. For example, in a block of six, for a two-arm trial, three subjects would be randomized to each group. If the block size is known or discovered, especially if masking is not possible, concealment of

the assignment of the last member of a block may not be possible. Use of permuted blocks—where a few different block sizes (eg, 4,6,6) are used but chosen randomly—helps to eliminate this form of deciphering.[15] Importantly, a block size of two should never be used because an investigator can guess the group assignment of half the subjects in an unmasked, two-arm trial. If, for example, in a given block of two, the last subject was allocated to placebo, the investigator knows the next subject will be allocated to treatment. The investigator can then preferentially enroll someone he/she would like to receive the treatment.

**An Important Distinction**

While we have reviewed the concepts of allocation concealment and masking (blinding) together, there are important distinctions. Masking only refers to the prevention of knowledge of assigned groups (as well as the allocation sequence) after actual allocation (B, C, and D in Figure 1). As such, the goal of masking is to prevent ascertainment bias.[13, 14] Allocation concealment, on the other hand, refers to the prevention of knowledge of upcoming assignment from the time of generation of the randomized sequence up until actual allocation (represented by A in Figure 1). The goal of allocation concealment is to prevent selection bias.[13, 14] While allocation concealment might seem complicated and cumbersome, it can always be incorporated into the design of an RCT. Masking, in contrast, cannot always be incorporated or carried out.[13, 14] For example, certain interventions (eg, cognitive behavioral therapy, certain surgeries) are extremely difficult to mask from subjects and their treating clinicians.

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