Methodology in Clinical and Health Services Research

Randomization and allocation concealment: a practical guide for researchers

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Abstract Although the randomized controlled trial is the most important tool currently available to objectively assess the impact of new treatments, the act of randomization itself is often poorly conducted and incompletely reported. The primary purpose of randomizing patients into treatment arms is to prevent researchers, clinicians, and patients from predicting, and thus influencing, which patients will receive which treatments. This important source of bias can be eliminated by concealing the upcoming allocation sequence from researchers and participants. Although there are many approaches to randomization that are known to effectively conceal the randomization sequence, the use of sequentially numbered, opaque sealed envelopes (SNOSE) is both cheap and effective. The purpose of this tutorial is to describe a step-by-step process for the preparation of SNOSE. We will outline how to prepare SNOSE to preserve allocation concealment in a trial that (*a*) uses unrestricted (simple) randomization, (*b*) stratifies randomization on one factor, (*c*) uses permuted blocks and, and (*d*) is conducted at more than 1 study site. © 2005 Elsevier Inc. All rights reserved.

1. Introduction

The randomized controlled trial (RCT) is widely accepted as being the most powerful tool currently available for ensuring the objective evaluation of the true benefits of medical care [1,2]. Although randomization itself is central to the internal validity of the RCT, the act of randomization is consistently poorly executed [3] and incompletely reported [4].

The primary purpose of randomizing patients into treatment arms is to prevent researchers, clinicians, and patients from predicting, and thus influencing, upcoming group assignments [5,6]. Concealing the knowledge of upcoming group assignments "prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given intervention group" (Definition of allocation concealment. CONSORT Statement Web site. Available at: http://www.consort-statement.org/allocation concealment.htm. Accessed March 1, 2005). It is well known that trials with inadequate or unclear concealment of the allocation sequence can produce up to 40% larger estimates of treatment effects [7].

Without exception, allocation concealment is achievable in all randomized trials, including animal experiments, bench research, and health services research [8,9]. There are many randomization methods that are known to effectively maintain allocation concealment; however, most are complex and expensive. Approaches such as pharmacy-controlled randomization, 24-hour central randomization offices (phone-in or Web-based), or even the use of numbered or

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coded containers in a placebo-controlled trial [10] require extensive infrastructure support that may be beyond the resources available to investigators in single-center trials. When conducted properly, randomizing participants using sequentially numbered, opaque sealed envelopes (SNOSE) is the most accessible and straightforward method of maintaining allocation concealment and does not require the use of specialized technology [11].

There are many published reports of attempts that have been made by individuals to subvert or decipher the allocation sequence in clinical trials. These attempts range in scale from break-and-enter, undertaken to obtain the master randomization list, to screening a sealed envelope using the x-ray viewing box to visualize its contents [3,10]. Clearly, no approach is immune to an individual dedicated to "break the code." However, if prepared with care, the use of SNOSE can be as reliable as any other method [11].

Although there are excellent papers that describe how a reader can critically appraise a published article to determine whether allocation concealment was maintained [10], there are very few detailed resources written for the clinical trialist or bench researcher. The purpose of this tutorial is to provide the clinical trialist and bench researcher with a simple but effective step-by-step process for the preparation of SNOSE. Although there are many ways to prepare SNOSE, the method we describe can be used to preserve allocation concealment in a trial that (*a*) uses unrestricted (simple) randomization, (*b*) stratifies randomization on one factor, (*c*) uses permuted blocks and, (*d*) is conducted at more than 1 study site.

Fig. 1   Preparation of envelope insert.

2. Materials required for a typical 50-patient trial

Obtain 50 identical, opaque, letter-sized envelopes; 50 sheets of standard-size paper; 25 letter-size sheets of single-sided carbon paper; and 2 rolls of household aluminum cooking foil. Complete the kit by purchasing a Tupperware-style plastic container large enough to hold all 50 envelopes.

2.1. Step 1: initial preparation

Cut the aluminum foil into 50 sheets that are of the same width as and twice the height of the envelope. The carbon paper should be cut into 50 envelope-sized sheets. Separate the 50 sheets of standard-size paper into 2 sets of 25 sheets. On one set of 25, print or write *Treatment A*, and on the second set, print or write *Treatment B*. If your trial is not blinded (treatment A vs treatment B), to avoid confusion, you should write the exact name of the assigned treatment (instead of *Treatment A* or *Treatment B*).

2.2. Step 2a: preparing treatment A envelopes

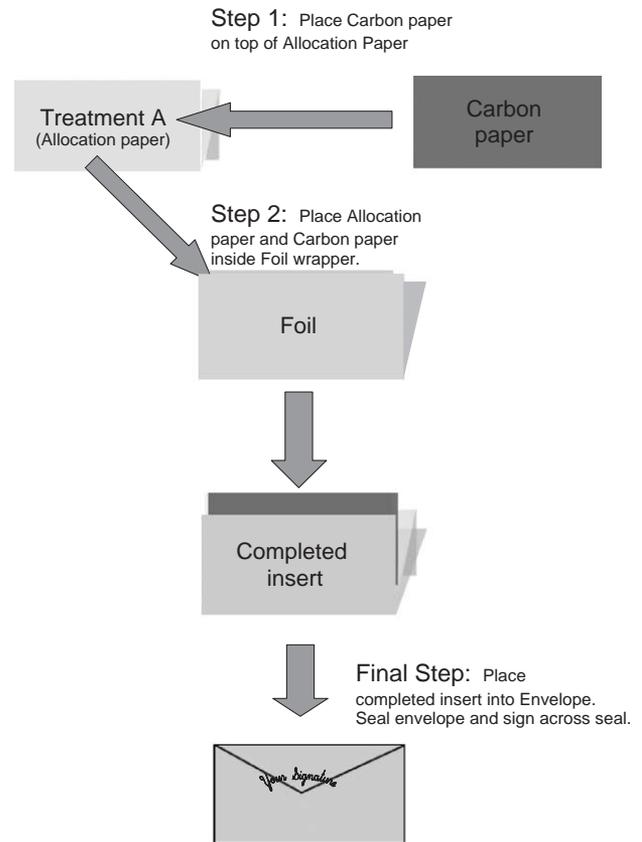Select 1 sheet of standard-sized paper marked *Treatment A* and fold to fit the envelope. Next, place 1 sheet of carbon paper on top of the folded treatment A allocation paper with the carbon side facing the paper (Fig. 1, Step 1) and fold 1. sheet of foil over both sides of the carbon–treatment A paper combination (Fig. 1, Step 2). Place the completed insert (Fig. 1) into a blank envelope, with the carbon paper closest to the front of the envelope.

If the completed insert is placed into the envelope properly, the double foil wrapper ensures that the envelope is truly opaque and cannot be read by holding it up against a strong light source [3,10]. If the carbon paper is positioned properly, writing on the front of the envelope is transferred to the actual treatment allocation paper inside. The carbon paper is important for establishing an audit trail that can be used to prevent violations of allocation concealment [11]. Complete all 25 treatment A envelopes, seal each envelope and sign your name, in pen, over the top of the envelope seal.

2.3. Step 2b: preparing treatment B envelopes

Prepare the treatment B envelopes as in step 2a. After step 2b is complete, there should be 1 pile of 25 sealed treatment A envelopes and a second pile of 25 sealed treatment B envelopes. Do not mix treatment A envelopes with treatment B envelopes and do not write on the envelopes, except for signing your name over the seal.

2.4. Step 3a: unrestricted (simple) randomization

Combine the 25 sealed treatment A envelopes with the 25 sealed treatment B envelopes and shuffle as you would a deck of cards. Once you are satisfied that the deck of envelopes is shuffled very thoroughly, with a firm hand, mark a unique number on the front of each envelope sequentially from 1 to 50, in pen. The carbon paper inside the envelope will transfer this number to the allocation paper inside. Place these envelopes into the plastic container, in numerical order, ready for use.

2.5. Step 3b: stratified randomization, 1 factor

Stratified randomization is used to ensure that important prognostic factors such as age, disease severity, or other patient characteristics are balanced across intervention groups [6]. For example, if we are studying a disease where it is widely accepted that smokers have a much worse outcome, then we could use stratification to ensure that similar numbers of smokers end up in each arm of the trial.

Because stratification has implications on analysis and increases the overall complexity of conducting the trial, it is counterproductive to stratify on a factor that may be related to outcome; the stratification factor must be known to be related to outcome. In addition, stratification should only be used if the trial is small enough that it is possible that all the patients with the prognostic factor could be randomized to receive only 1 treatment (ie, all patients who receive treatment A are smokers and none of the patients who receive treatment B are smokers). Although there is no absolute cut-off, trials with more than 200 subjects likely do not benefit from stratification [12].

In this example, we will stratify on the presence of 1 factor (smoker/nonsmoker) at the time of randomization. For the sake of simplicity, let us assume that we know exactly how many smokers and nonsmokers will be enrolled.

First, create and seal 25 treatment A envelopes and 25 treatment B envelopes as outlined in steps 1, 2a, and 2b. Next, obtain 2 Tupperware-style plastic containers and mark one *Smoking strata* and the other *Nonsmoking strata*.

For the sake of simplicity, assume that previous research documents that 40% of the potential participants will be smokers. If we enroll 20 smokers into our 50-patient trial, the trial population will be representative of the known patient population. To prepare for enrolling a total of 20 smokers, select 10 treatment A envelopes and 10 treatment B envelopes and shuffle thoroughly. Once you are satisfied that the deck of 20 envelopes is shuffled very thoroughly, mark a unique identifier on the front of each envelope sequentially from 1-S to 20-S. The carbon paper inside the envelope will transfer this identifier to the allocation paper inside. Place these 20 envelopes, in numerical order, in the container marked *Smoking strata*, ready for use.

To prepare the nonsmoking strata, select the remaining 15 treatment A and 15 treatment B envelopes. Shuffle these 30 envelopes as with a deck of cards. Once you are satisfied that the deck of envelopes is shuffled very thoroughly, mark a unique identifier on the front of each envelope sequentially from 1-N to 30-N. Place these 30 envelopes, in numerical order, in the container marked *Nonsmoking strata*, ready for use. Do not forget to tell your research team to choose an envelope from the smoking strata container if the patient is a smoker. Otherwise, they should choose an envelope from the nonsmoking strata container.

This example assumes that you are certain that you will enroll a total of 50 patients in your trial, with 20 smokers and 30 nonsmokers. If you are uncertain as to what the actual number of patients in each strata will be before beginning your trial, we recommend you use permuted blocks within each strata to ensure balance between your main treatment arms (see step 3c).

2.6. Step 3c: permuted block randomization in a stratified trial

Block randomization is simply a process that can be used to ensure balance in a clinical trial after the enrollment of each *block* of patients. In step 3a, because we prepared 25 treatment A envelopes and 25 treatment B envelopes, at trial completion (after enrolling 50 patients) we would be certain of having similar numbers in each group. What if the trial is stopped after 12 patients? How could we ensure balance in this situation? By selecting a block size of 4, we are simply ensuring that after every fourth patient is enrolled, 2 will have received treatment A and 2 will have received treatment B.

Permuted blocks are useful for maintaining similar treatment group sizes in small, stratified, or multicentered trials when the number of patients who will be recruited within each strata, or center, is uncertain. Unfortunately, recent research suggests that it may be possible to subvert or anticipate the randomization sequence in unblinded trials that are block-randomized using a uniform block size [12]. For this reason, we strongly recommend using at least 2 or more different block sizes.

The remainder of this example will guide you through the process of preparing a randomization kit for a 50-patient RCT, stratified on 1 factor (eg, presence of sepsis, yes/no), where we are uncertain exactly how many patients will be septic at the time of recruitment. To account for this uncertainty, we will block-randomize within strata using 2 different block sizes (4 and 6).

In previous examples, we created exactly 50 envelopes for our 50-patient trial. In this example, although we still intend to conduct a 50-patient trial, we will need to prepare more than 50 envelopes. If we assume, based on an educated guess, that the maximum number of patients who could possibly be recruited into either of the 2 strata would be 40, to be safe, a total of 80 envelopes should be prepared and sealed. Repeat steps 1, 2a, and 2b to prepare 40 treatment A envelopes and 40 treatment B envelopes. It is much better to prepare more envelopes than to run out halfway through the trial.

As with step 2b, obtain 2 Tupperware-style plastic containers and mark one *Sepsis strata* and the other *No-Sepsis strata*. To prepare the envelops required to randomize up to 40 patients in the sepsis strata, select 20 treatment A envelopes and 20 treatment B envelopes and place them in separate piles. Do not mix these piles yet. In the next step, we will create blocks of 4 and 6.

2.6.1. Creating blocks

To create a block of 4, select 2 treatment A envelopes and 2 treatment B envelopes. Shuffle these 4 envelopes thoroughly, and place this block of 4 in a separate pile (Fig. 2). To create a block of 6, choose 3 treatment A envelopes and 3 treatment B envelopes. Shuffle these 6 envelopes thoroughly and place this block of 6 in a separate pile. Do not mix the block of 6 with the previously created block of 4 yet. Keep preparing additional blocks of 4 and 6 until all 40 treatment A and B envelopes have been used. All additional blocks should be placed in their own individual piles. You should have 4 individual piles of shuffled blocks of 4 and 4 individual piles of blocks of 6. Next, we will combine these 8 individual piles.

Remember, the reason for using 2 different block sizes is to ensure the allocation sequence cannot be anticipated. Because of this, it is important that you do not simply combine the blocks by alternating between a block of 4 and a block of 6. We suggest that you allow the order of the blocks to be determined by flipping a coin (the original random number generator!).
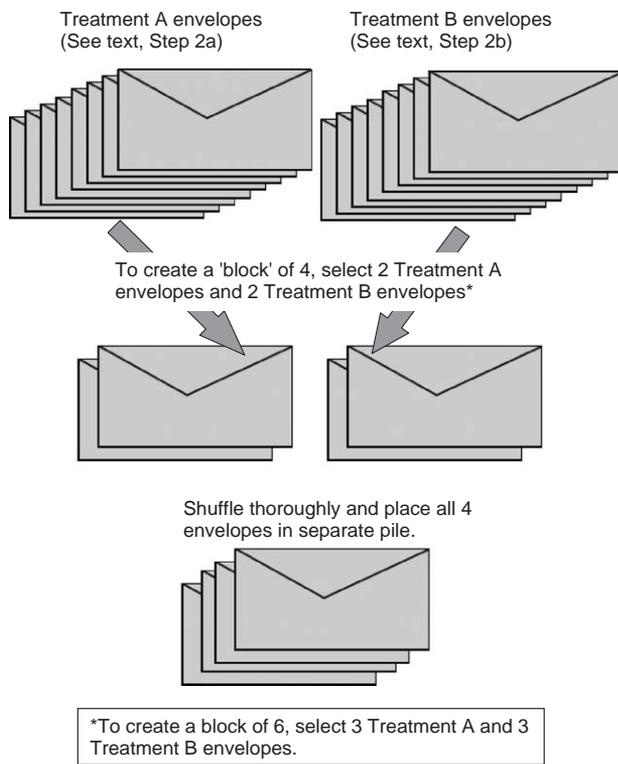

Treatment A envelopes (See text, Step 2a)   Treatment B envelopes (See text, Step 2b)

To create a 'block' of 4, select 2 Treatment A envelopes and 2 Treatment B envelopes*

Shuffle thoroughly and place all 4 envelopes in separate pile.

*To create a block of 6, select 3 Treatment A and 3 Treatment B envelopes.

Fig. 2   Permuted block randomization (blocks of 4 and 6).

2.6.2. Flip the coin

If the coin lands head, select 1 block of 4. If the coin lands tail, begin with a block of 6. Flip the coin again. If the coin lands head, select another block of 4 and place it on top of the first block, or if it lands tail, select a block of 6 and place it on top of the first block. Repeat this process until all 40 envelopes are in 1 single pile. Do not mix or shuffle this new pile; otherwise, you will break your block randomization pattern.

Once all 40 envelopes are in a single pile, mark a unique identifier on the front of each envelope sequentially from 1-S to 40-S. Place these 40 envelopes, in numerical order, in the container marked *Sepsis strata*, ready for use.

To prepare the no-sepsis strata container, repeat the process outlined for the sepsis strata, except that these envelopes should be numbered sequentially from 1-N to 40-N. Place these 40 envelopes, in numerical order, in the container marked *No-Sepsis strata*, ready for use.

Do not forget to tell your research team to choose an envelope from the sepsis strata container if the patient has sepsis at the time of randomization. Otherwise, they should choose an envelope from the no-sepsis container.

2.7. Step 3d: permuted blocks in a stratified trial with 2 (or more) study sites

In this example, the 50-patient trial will be conducted at 2 sites, will be stratified on 1 factor (sepsis/no-sepsis), and will use permuted block randomization within strata.

First, based on your best guess, estimate the maximum number of patients any one site will enroll in any single strata. Because it is better to overestimate than to run out of envelopes halfway through the trial, if we assume that the maximum number of patients who could possibly be enrolled in any one strata from 1 site is 40 patients, a total of 160 envelopes (80 treatment A and 80 treatment B) should be prepared.

To set up the randomization kit for site 1, repeat steps 1, 2a, and 2b as if an 80-patient trial were being conducted. Repeat step 3c as if 40 patients will be enrolled in the sepsis strata and 40 patients will be enrolled in the no-sepsis strata. For site 2, repeat steps 1, 2a, and 2b as if an 80-patient trial were being conducted. Step 3c would be repeated assuming 40 patients will be enrolled into each stratum at site 2. Note that 4 Tupperware-style plastic containers will be required to hold the randomization kits for this study: site 1 will require a container each for the sepsis and no-sepsis strata patients and site 2 will also require 2 containers (sepsis and no-sepsis).

3. Additional notes on blocking

Block randomization will not guarantee that an identical number of patients will be enrolled into each arm of the trial, but it will ensure that similar numbers of patients are enrolled into each arm. There are no requirements that group sizes must be identical, merely similar [12]. Furthermore, it is not

essential that your chosen block sizes divide evenly into your group size. In our examples, 4 blocks of 4 and 4 blocks of 6 conveniently adds up to 40 patients. We could have chosen to use 5 blocks of 4, 3 blocks of 6, and accounted for the final 2 patients in a block of 2. In fact, any combination of sizes would work. The primary purpose of varying the block size is to prevent the study participants from guessing the upcoming randomization sequence.

4. Study start-up meeting/research team education sessions

Every clinical trial or laboratory experiment must have a formal start-up meeting or educational session. Anyone who will enroll and randomize patients must be formally taught how the study is to be conducted. At the start-up meeting, take time to emphasize that study randomization envelopes must always be opened sequentially (from lowest to next highest number). Before opening, make sure the research team member writes the patient's study identifier (patient study number), the date, and their signature on the front of the envelope. Inform your research team that the carbon paper inside the envelope will transfer both the patient identifier, date, and their signature to the treatment allocation paper inside. Provide the research team with practice envelopes so that they can learn exactly how hard to press when they write on the front of the envelope to ensure that all information is transferred to the treatment allocation paper inside. Make sure they know that this treatment allocation paper must be kept and will be audited at the end of the trial.

The primary purpose of setting up this audit trail is not so that you can detect any subterfuge at the end of the trial. It is so that you can convince your research team that you will be able to detect any subterfuge and thus prevent it from occurring. Finally, although international guidelines exist that outline record retention and reporting policies for licensing trials conducted in some geographic areas (See ICH GCP Web site. Available at: http://www.ich.org. Accessed April 4, 2005), the trialist should be aware of their own national body and regional human and/or animal research ethics committee requirements.

5. Conclusion

The primary purpose of randomizing patients into treatment arms of a clinical trial is to make the allocation sequence unpredictable. Although there are many ways that patients can be randomized into a clinical trial so that the allocation sequence is concealed, most require a methodologist and are expensive. This article describes 1 method for the preparation of SNOSE that is simple, cheap, and effective. The use of SNOSE can be described in a paper's methods section in an extremely efficient manner: patients were randomized to treatment groups using SNOSE.

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Commentary

Maintaining allocation concealment: following your SNOSE

The major threat to the internal validity of any intervention trial is the possibility that unwanted differences between groups, due to either random chance or bias, may interfere with the ability of researchers to measure a true effect. Chance differences between groups are never possible to avoid completely but can be made less likely by ensuring that a study has an adequate sample size. On the other hand, bias, or systematic error, can be introduced either intentionally or unintentionally and is far more likely to interfere with study execution and interpretation of results. Unfortunately, bias is also much more difficult to avoid.

The most accepted and reliable methodology for reducing unwanted bias in a clinical trial is the randomization technique. As outlined in the CONSORT statement [1], randomization offers 3 major advantages: (1) it eliminates