

Methodology in Clinical and Health Services Research

Randomization and allocation concealment:

A practical guide for researchers

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Summary

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 sealed, opaque sequentially numbered 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 randomisation on one factor; c) uses permuted blocks and; d) is conducted at more than one study site.

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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: <http://www.consort-statement.org/allocationconcealment.htm>. Accessed 1/3/2005). 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 coded containers in a placebo controlled trial (10) require extensive infrastructure support that may be beyond the resources available to investigators in single-centre 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 specialised 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, in order to visualise 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 paper 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 randomisation on one factor; c) uses permuted blocks and; d) is conducted at more than one study site.

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 two rolls of household aluminium cooking foil. Complete the kit by purchasing a tupperware-style plastic container large enough to hold all 50 envelopes.

Step 1: Initial preparation

Cut the aluminum foil into 50 sheets that are the same width as the envelope, and twice its height. The carbon paper should be cut into 50 envelope sized sheets. Separate the 50 sheets of standard size paper into two 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 B).

Step 2a: Preparing Treatment A envelopes

Select one sheet of standard sized paper marked "Treatment A" and fold to fit the envelope. Next, place one sheet of carbon paper on top of the folded Treatment A allocation paper with carbon side facing the paper (Figure 1, Step 1) and fold one sheet of foil over both sides of the carbon-Treatment A paper combination (Figure 1, Step 2). Place the completed insert (Figure 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 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 top of the envelope seal.

Step 2b: Preparing Treatment B envelopes

Prepare the Treatment B envelopes as in Step 2a. After Step 2b is complete, there should be one 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.

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 one to fifty, 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.

Step 3b: Stratified randomization, one 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. Additionally, 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 one treatment (i.e. 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 one factor (smoker / non smoker) at the time of randomization. For the sake of simplicity, let us assume that we know exactly how many smokers and non-smokers will be enrolled.

First create and seal 25 Treatment A envelopes and 25 Treatment B envelopes as outlined in Step 1, Step 2a and Step 2b. Next, obtain two tupperware-style plastic containers and mark one "Smoking strata" and the other "Non Smoking strata".

For the sake of simplicity, assume that previous research documents that 40% of the potential participants will be smokers. If we enrol 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 Non Smoking 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 Non Smoking strata, ready for use. Don't 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 Non-Smoker strata container.

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

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 enrolment 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, two will have received Treatment A and two will have received Treatment B.

Permuted blocks are useful for maintaining similar treatment group sizes in small, stratified, or multi-centred, trials when the number of patients that will be recruited within each strata, or centre, 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 two 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 one 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 two different block sizes (four and six).

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 that could possibly be recruited into either of the two strata would be 40, to be safe, a total of 80 envelopes should be prepared and sealed. Repeat Step 1, Step 2a and Step 2b to prepare 40 Treatment A envelopes and 40 Treatment B envelopes. It is much better to prepare MORE envelopes than to run out half way through the trial.

As with Step 2b, obtain two tupperware-style plastic containers and mark one "Sepsis strata" and the other "No Sepsis strata". To prepare the envelopes 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 four and six.

Creating blocks.

To create a block of four, select two Treatment A envelopes and two Treatment B envelopes. Shuffle these four envelopes thoroughly and place this 'block of four' in a separate pile (Figure 2). To create a block of six, choose three Treatment A envelopes and three Treatment B envelopes. Shuffle these six envelopes thoroughly and place this 'block of six' in a separate pile. Do not mix the block of six with the previously created block of four yet. Keep preparing additional blocks of four and six 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 four

individual piles of shuffled blocks of four and four individual piles of blocks of six. Next we will combine these eight individual piles.

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

Flip the coin.

If the coin lands heads, select one block of four. If the coin lands tails, begin with a block of six. Flip the coin again. If the coin lands heads, select another block of four and place it on top of the first block, or if it lands tails, select a block of six and place it on top of the first block. Repeat this process until all 40 envelopes are in one 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 above, except 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 at Randomization, ready for use.

Don't 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.

Step 3d: Permuted blocks in a stratified trial with two (or more) study sites

In this example, the 50 patient trial will be conducted at two sites, will be stratified on one 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 enrol in any single strata. Because it is better to over-estimate than to run out of envelopes half way through the trial, if we assume that the maximum number of patients that could possibly be enrolled in any one strata from one 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 Step 1, Step 2a and Step 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 Step 1, Step 2a and Step 2b as if an 80 patient trial were being conducted. Step 3c would be repeated assuming 40 patients will be enrolled into each strata at Site 2. Note that four 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 two containers (Sepsis and No Sepsis).

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, four blocks of four and four blocks of six conveniently adds up to 40 patients. We could have chosen to use five blocks of four, three blocks of six and accounted for the final two patients in a 'block of two'. 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.

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 enrol 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 (next highest number). Prior to 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 geographical areas, (See ICH GCP web site: <http://www.ich.org>, Accessed 4/4/2005) the trialist should be aware of their own National body and regional Human and/or Animal Research Ethics Committee requirements.

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 paper describes one 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 sequentially numbered, opaque sealed envelopes.

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Figure 1: Preparation of envelope insert

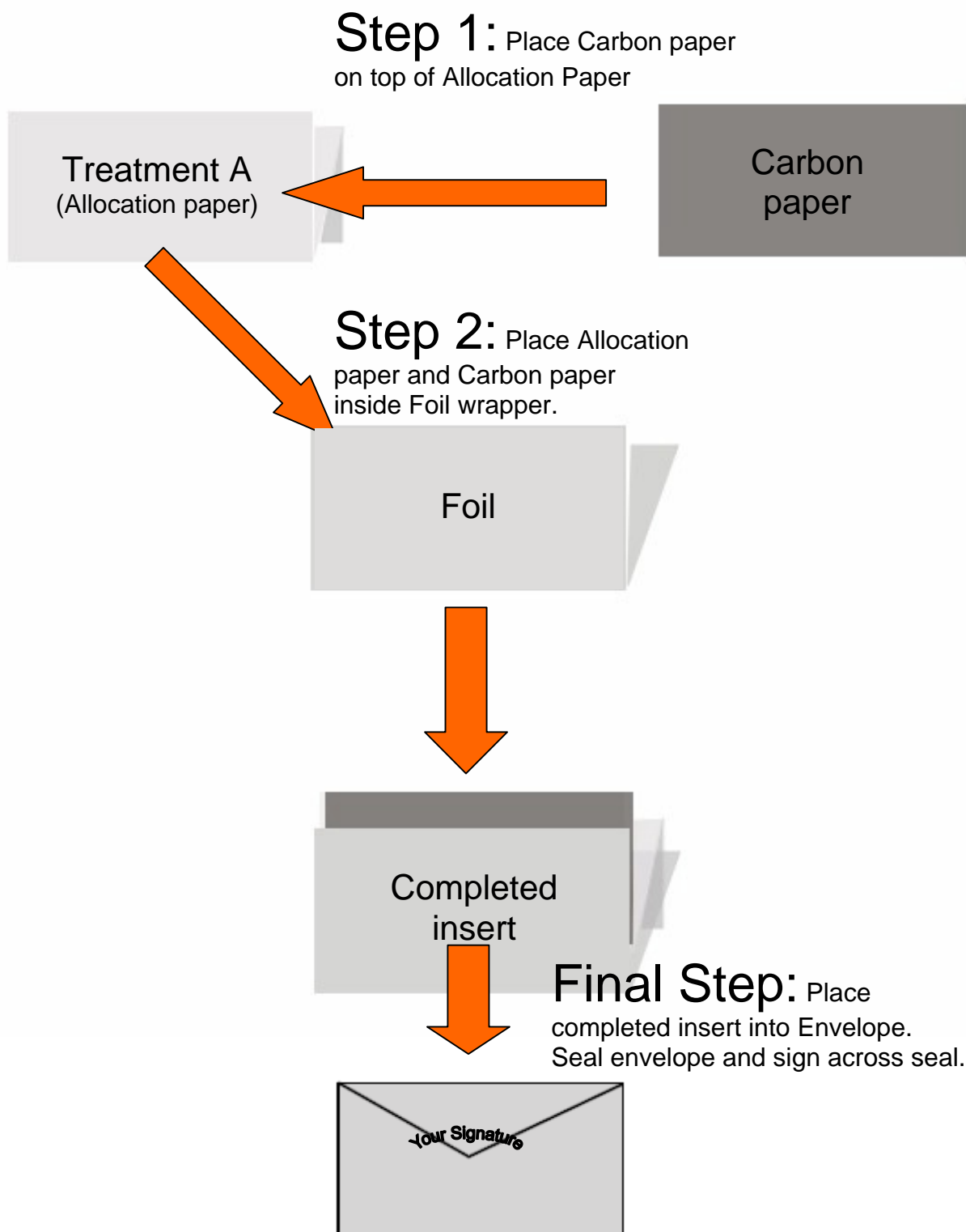
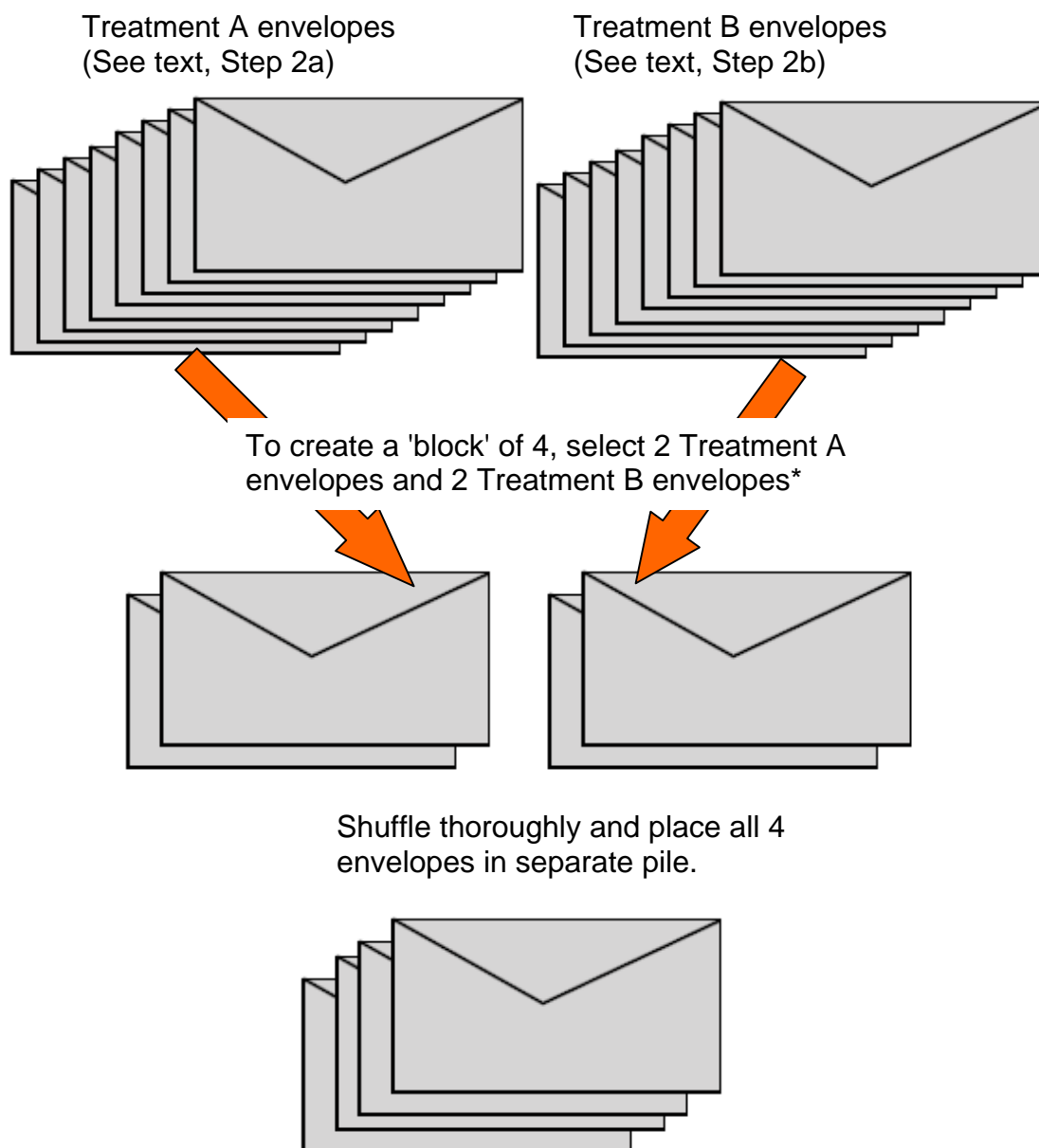


Figure 2: Permuted block randomization (blocks of 4 and 6)



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