**Allocation concealment in randomised controlled trials: could do better**

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*Separating the act of randomisation from the person recruiting a trial participant is the keystone for a robust randomised controlled trial. Much methodological research has demonstrated that randomisation could be subverted by researchers or clinicians if the possibility exists. Consequently, for a RCT to be robust methods must be used to ensure that allocation subversion is difficult or impossible. However, in a sample of 79 trials published in major medical journals in June-August 2015 a large proportion (19%) used suboptimal allocation concealment, which undermines their rigour. Journals should specify that in future, trials will not be published if they used sub-optimal allocation methods. Furthermore, trials that use blocked randomisation should statistically test whether or not there is a relationship between block position and outcome.*

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Exaggerated treatment effects among randomised controlled trials (RCTs) using poor randomisation methods have been found numerous times[[1]](#endnote-1),[[2]](#endnote-2). We investigated the impact of including poorly randomised trials in meta-analyses[[3]](#endnote-3) and found that nine of 12 systematic reviews of RCTs, published in key medical journals, had age heterogeneity between randomised groups. The only reasonable explanation for this is that the randomisation process ‘failed’ among some included RCTs, which questions the reviews’ reliability.

*Successful randomisation*

Randomisation will form groups that are equivalent in both known and unknown variables, apart from chance differences. This should be achieved when robust sequence generation and adequate allocation concealment methods are used. All trials can have adequate allocation concealment[[4]](#endnote-4), where the randomisation sequence is unknown to the recruiting party until the point at which the participant is randomised. The CONSORT statement, which the leading medical journals endorse, states that the method of allocation (sequence generation, allocation concealment mechanism, and implementation) should be clearly described4. Allocation concealment can be made more or less difficult by the method of allocation sequence generation as well as the concealment mechanism.

*Sequentially Numbered Opaque Sealed Envelopes (SNOSE)*

In the SNOSE system, envelopes containing the treatment allocation are opened by the recruiting clinician upon participant enrollment. For this approach to be robust, certain criteria should be fulfilled. First, the envelopes should be truly opaque and sequentially numbered. Second, the clinician should not open the envelope in advance of participant enrolment, and should ensure the envelope seal has not been broken before they use the envelope to randomise a participant. However, even with opaque, sequentially numbered envelopes where the order of participant recruitment and envelope opening are in concordance, we cannot guarantee envelopes were not opened in advance to allow strategic scheduling of patient appointments so that patients are matched with the recruiter’s preferred allocation for them. For example, a surgical trial found three out of five surgeons opened envelopes in order to subvert the randomisation[[5]](#endnote-5). It has been shown that trials that use the SNOSE method are more likely to show a statistically significant treatment effect than trials that use more secure allocation methods2. Despite this, the Cochrane handbook of systematic reviews suggests that trials that use SNOSE have a low risk of bias[[6]](#endnote-6). In practice, the bias risk is only lessened or eliminated when the individual(s) with access to the envelopes is distinct from the individual(s) recruiting participants to the trial.

*Blocked randomisation*

Most trials use restricted randomisation, such as stratification[[7]](#endnote-7), which requires the use of block allocation within each strata to distinguish it from simple randomisation. Even if a robust allocation concealment mechanism is used (e.g., central web-based randomisation), subversion of the allocation may be possible when certain restricted methods of allocation sequence generation are used. For instance, stratifying by site (in a multi-site trial) and using a small fixed block size will render the allocation sequence predictable7. For example, in a two arm trial using randomisation stratified by site and a fixed block size of four, every fourth allocation can be predicted with perfect accuracy, and the third allocation in a block can be accurately predicted a third of the time. Indeed, only simple randomisation avoids the problem[[8]](#endnote-8) that simply guessing that the next allocation will be the opposite of the previous one will be correct more often than not. This is not just a theoretical concern. For example, Engel and colleagues,[[9]](#endnote-9) noted that in some recruiting centres for a trial of supplemental oxygen for retinopathy of prematurity, recruitment rates fell after an intervention assignment. Clinicians were trying to avoid recruiting and allocating patients when they thought they could predict the next assignment to be to the control group which they judged, for a given patient, as being undesirable. A RCT of rehabilitation for patients with fractured neck of femur failed because, despite using telephone randomisation, the block size of 6was deciphered part way through the trial which led to prediction and selection bias[[10]](#endnote-10). The use of larger and/or variable blocks sizes or avoiding stratifying by site in a multi-site trial will minimise this problem. Note, however, a common strategy of mixing a block size of four with a block size of two will actually improve allocation prediction relative to use of a fixed block size of four and make potential subversion worse. Better still, the use of simple randomisation for large trials (n>100) has been advocated7.

Minimisation is an alternative method of restricted randomisation which allocates participants to the trial arm that best maintains balance across specified stratifying factors[[11]](#endnote-11). Minimisation is a dynamic mode of random allocation in that instead of being allocated to the next allocation in a pre-generated list, a subject’s allocation depends on their characteristics and, crucially, the characteristics of the participants already enrolled. Allocation by minimisation is much more difficult to predict than stratified, block randomisation, particularly if a random element is introduced.

In certain trial designs, such as double-blind, placebo controlled trials, these issues are mostly irrelevant. If the randomisation process simply involves assigning the participant with a number corresponding to a packet of drugs, and only the pharmacist has access to the unblinding codes, then allocation concealment is far less of a concern.

Given the evidence it would be hoped that all trials now employ secure allocation concealment methods. We reviewed the allocation concealment methods of recently published trials to investigate whether practices have improved since a previous analysis in 2002. 2

*Current trials*

We hand searched four high impact medical journals (*British Medical Journal (BMJ); Journal of the American Medical Association (JAMA); The Lancet;* and *the New England Journal of Medicine (NEJM))* for individually randomised controlled trials published between June and August 2015. We extracted, and judged, their mechanism for ensuring allocation concealment. We took into consideration the study design, method of generating the allocation sequence, and the process of how a participant was assigned to a treatment group when formulating a judgement. We defined *adequate* allocation concealment as the description of a process that made it unlikely for the allocation to be predicted. The use of envelopes, or randomisation stratified by site with small block sizes (e.g., two or four) even if the allocations were centrally conducted through the web or telephone, was deemed inadequate except in double blind trials. It is noteworthy that this information was not always easy to ascertain from reading the trial publication. Where insufficient detail in the paper was provided, we sought out details in the protocol or emailed the authors.

We identified 79 individually randomised controlled trials published between June and August 2015 in the *BMJ, JAMA, The Lancet;* and *the New England Journal of Medicine*. Of these, 27 (34%) were placebo controlled double blind trials making it difficult, if not impossible, to decipher the allocation. We judged these trials as adequate, as well as a further 22 (28%) open trials. We found, initially, that 13 trials (16%) had used a randomisation method that put them at risk of bias with another two trials being found to be inadequate after correspondence with the authors (Table): seven used envelopes to allocate participants, seven trials stratified by site using small block sizes and one used both small blocks and envelopes. In the table we describe the randomisation procedure described for the 15 trials and our concerns about the allocation. For example, a trial by Senn and colleagues[[12]](#endnote-12) stratified by three centres using “permuted blocks of two”. If the researchers at a site deduced that a block size of two was being used, then accurate prediction of every other allocation would have been possible.

We, initially, judged 17 (22%) open trials as unclear, because poor reporting meant there was insufficient detail to determine whether the method of allocation concealment was adequate, e.g. no further detail given except: “*Eligible patients were randomly assigned in a 1:1 ratio to receive either elotuzumab in combination with lenalidomide and dexamethasone (elotuzumab group) or lenalidomide and dexamethasone alone (control group)”*[[13]](#endnote-13). Of the 17 unclear trials we received responses from the authors of nine (53%) trials to our email requests for more information.

We spotted two interesting inconsistencies with the use of block randomisation. In the Senn trial there was an imbalance of 12 participants between randomised groups (464 in the intervention group, and 452 in the control), when the largest possible imbalance for such a procedure is three. Correspondence with the authors confirmed that for 10 cases misallocation had occurred with all 10 mis-allocations being assigned to the intervention group.[[14]](#endnote-14). Second, Cox and colleagues[[15]](#endnote-15) stated the following: *“randomly allocated them 2:1 to receive… The allocation sequence list, with blocks of four…”.* However, when using a 2:1 allocation ratio with blocking, the block sizes should be divisible by three (e.g., 3, 6 etc). Correspondence with the author confirmed that the statement in the paper of block size of four was a mistake and an erratum has been published in *The Lancet*.

**Discussion**

We found 19% of trials published in our sample described inadequate methods of allocation concealment, and a further 22% failed to report their randomisation methods clearly. These proportions are similar to those found in a review of RCTs published in the same journals in 2002 (18% and 26% that were inadequate and unclear respectively), although in the earlier review the sample size of studies was much larger (January-December 2002, n=234) than the current review (n=79). Randomisation and allocation concealment details are staple methodological aspects which we should expect to be clearly reported within RCT publications.

Despite the known inadequacies of the use of envelopes for treatment allocation, we found their use in at least 10 trials. For instance a trial of remote ischemic preconditioning on kidney injury[[16]](#endnote-16) states that: “*Randomization codes were computer generated and concealed from the investigators”* and in the accompanying protocol it states *“It will be performed using sealed envelopes.”*  It does not matter whether the allocation code is computer generated or the investigators are blinded if the person enrolling the patient can potentially open an envelope in advance. We appreciate that in certain scenarios, such as trials conducted in remote areas, the use of SNOSE may be the only feasible approach: if so they should be sequentially numbered and it should be stated clearly that a person who is separate from the assessment and recruitment of the patient opens the envelope as described in the CONSORT statement (item 10)4. Rigour might be further enhanced by writing patients details on the outside of the envelope which are transferred to the allocation inside *before* the envelope is opened.

One way forward would be for leading medical journals to specify that trials that use small block sizes (e.g., smaller than six with stratification by site) and/or SNOSE will not be accepted for publication from 2020, unless there are extreme extenuating circumstances (e.g., emergency medicine, location of trial). Leading medical journals did something similar for trial registration, which has led to a sea of change in this area. If, however, these methods are used explicit and transparent methodological details should be insisted upon. Meanwhile journals could request the trials that used blocked randomisation perform a Berger-Exner test[[17]](#endnote-17) to assess for selection bias. This statistical test looks for a relationship between baseline variables and the position of the participant in the block. In the absence of subversion there should be no relationship between these factors. This is not onerous for the authors and would demonstrate their trial was conducted with robust methodology. Refusal to undertake such a test would preclude publication. Whilst some trials[[18]](#endnote-18),[[19]](#endnote-19) that use block randomisation do report checking for subversion, use of this statistical approach is rare.

Journals should also ask a methodologist to carefully review the reported methods of randomisation before any trial is published or even sent for wider review. If those planning future trials felt the option of publication in a high impact journal was closed to them if their randomisation system was not robust then this would focus minds at the design stage, it would also lead to an awareness and education in the importance of robust randomisation methods and clearer reporting. Although it is welcome that journals are endorsing CONSORT the enforcement of this is inadequate. We propose that for randomisation at least that an editor or reviewer is mandated to inspect the form of words used to ensure that they are CONSORT compliant.

**Key messages**

Good allocation concealment is vital for robust randomised trials.

38% of trials the trials examined in this sample and published in major medical journals do not report good allocation concealment methods.

Journals should insist that sealed envelopes and other weak concealment methods are no longer to be used.

**Advice for researchers**

* Consult with a methodologist when designing a RCT.
* Explicitly state randomisation and allocation concealment methods in protocol and publication. If there is a reason why the information cannot be provided in the publication (for example the word limit) refer to the section of the protocol in which a reader can find it, or supply the information in a supplementary document.
* Use simple randomisation for larger sample sizes and consider using minimisation if stratification is required.
* When calculating costings for a RCT, factor in funding for third party randomisation services.
* If SNOSE are the only practical method to conceal the randomisation sequence ensure that their preparation and execution is methodologically rigorous – state who prepared the envelopes, what (if any) additional security measures were in place, and who opened the envelopes in the publication of the RCT.
* Transparently report randomisation and allocation concealment methods in sufficient detail for readers.

**Advice for Funders**

* Ensure a methodologist is involved in designing and reporting the RCT
* Do not fund RCTs using SNOSE unless justified as the only available option
* Do not fund research where blocking of a size of less than 6 is used with site stratification

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**Table showing reason and rationale for classification of inadequate concealment**

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| --- | --- |
| **Author and randomisation/allocation concealment details**  | **Rationale [author response if contacted]** |
| **\*Smith et al, 2015 BMJ\*\****After informed consent was obtained, the first study pain score was recorded using a visual analogue scale, and the participant was randomised (using a secure web based randomisation system) to receive either PCA or routine care.* | Web based randomisation but no description of type of randomisation (e.g.,whether blocking was used). [**Contact with authors confirmed use of mix of block sizes of 2 and 4, which was kept secret from recruiting staff**] – the use of a mixture of blocks of 2 and 4 lead to an 88% chance of prediction using the technique of assuming the next allocation was the opposite of the previous one. |
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| **Detollenare et al, 2015 BMJ***The women were randomly allocated in a 1:1 ratio using a web based application with computer generated randomisation tables in blocks of four, stratified by hospital and stage of uterine prolapse*. | Web randomisation but stratified by centre using blocks of 4 – leads to predictability. |
| **Salimen, 2015, JAMA***Patients were randomized by a closed envelope method either to undergo open appendectomy or to receive antibiotic therapy with intravenous ertapenem. The randomization was performed with a 1:1 equal allocation ratio. There were 610 opaque, sealed, and sequentially numbered randomization envelopes. The envelopes were shuffled and then distributed to each participating hospital. To randomize a patient, the surgeon on duty in each participating hospital opened a consecutively numbered envelope that contained information regarding the randomization group assignment for the patient. Most of the treating surgeons were not part of the core study team and provided care as they did in their normal clinical practice.* | Use of envelope opened by recruiting clinician also in report authors state shuffling sequentially numbered envelopes, this would break the numerical sequencing. [**On contacting the author the author clarified that the shuffling of the envelopes was performed prior to the sequential numbering.]** |
| **Stéphan 2015, JAMA***Randomization was conducted in blocks of 2 or 4, regardless**of entry criteria, with opaque envelopes, with a single computer-generated (nQuery Advisor) random-number sequence for all centers. Attending physicians randomly assigned patients in a 1:1 ratio to one of the 2 groups.* | Envelopes used with small block sizes with clinicians recruiting patients opening the envelopes. Mix of blocks of 2 and 4 leads to a high (88%) chance of prediction. |
| **Polusny et al, JAMA 2015***Randomization was conducted using SAS PROC PLAN in**blocks of 4 to ensure even randomization across the length of the study. A restricted electronic randomization chart was provided to the study coordinator by the statistician.* | Unclear, contacted authors. In protocol state minimisation and envelopes to be used, and in paper blocks of 4. Response from authors still does not clarify whether envelopes were used or not. **[Randomization was done as was described in the paper. We did deviate from the protocol in that we did not block on CAPS security. We assumed that, given that a CAPS based diagnosis of PTSD was necessary for entry into the study, that symptom levels would be sufficiently high across the sample and that randomization would give us an even distribution of severity. We also used a restricted access randomization chart (this was done in Excel with a separate sheets containing the randomization information for each subject) which I created and only myself and the study coordinator had permissions to access]**. |
| **Klingberg-Allvin, 2015 Lancet***Eligible women who consented to participation were randomly allocated to a midwife (intervention) or a physician (standard care [control]) for diagnosis and treatment. The randomisation (1:1) was done in blocks of 12 and was stratified for study site. We used a computer random number generator to generate a list of codes from 1 to 994 and each code was linked to one of the two study groups. Sequentially numbered, opaque, sealed envelopes, each containing a random allocation, were prepared at the coordinating centre, and later opened in consecutive order by the research assistants after obtaining written consent*. | Use of envelopes is an inadequate method. Also it is unclear if the research assistants prepared and opened the envelopes to recruit participants |
| **Broekhuijsen 2015, The Lancet** *We randomly assigned participants (1:1) to immediate delivery or expectant monitoring. The randomisation was done with a web-based system by random permuted blocks with variable block size (range 2–4), stratified by centre.* | Centre stratification with blocks of 4 & 2 lead to high risk of prediction (88%). |
| **Ardehali 2015, The Lancet***Participants eligible at the second assessment were randomly assigned (1:1) to receive donor hearts preserved with either the Organ Care System or standard cold storage. An independent biostatistician prepared sealed and masked randomisation envelopes, which were assigned to each trial site. Participants, investigators, and medical staff were not masked to group allocation.* | Use of envelopes is an inadequate method. Also it is unclear who opened the envelopes – if recruiting clinician this increases risk of bias. |
| **Ngandu, 2015, The Lancet***We randomly assigned participants into the intensive multidomain intervention or regular health advice group (referred to as control group) in a 1:1 ratio. Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site after baseline by the study nurse.* | Small block size (4) with centre stratification using an open design allows the risk of bias due to prediction of allocation. |
| **Barone et al, 2015, Lancet***The allocation sequence was computer generated centrally at WHO and enrolment and randomisation was done by a research assistant based at each study site. Randomisation was in a 1:1 ratio, stratified by country, and restricted with randomly varying block sizes of 4–6. We concealed allocation through sealed opaque envelopes. Randomisation envelopes were opened by study staff just before random assignment.* | Envelopes opened by study staff who were recruiting participants.  |
| **Arabi, 2015,** **New England Journal of Medicine***Enrolled patients were randomly assigned to the permissive-underfeeding group or the standard feeding group with the use of opaque, sealed, sequentially numbered envelopes. The randomization list was computer-generated. Randomization was performed in random permuted blocks and was stratified according to center.* | Use of envelopes increases risk of bias by advanced opening of envelopes. No description of block size.  |
| **Senn, 2015 New England Journal of Medicine***At the baseline session, participants completed a computerized**survey, underwent randomization, and immediately attended their first resistance session or a control session. Randomization was performed in permuted blocks of two with the use of the online tool Randomize.net, with stratification according to site.* | A block size of only two allows a 75% prediction rate for future allocations assuming strategy of guessing the next allocation is always the opposite of the previous one. Furthermore, given a block size of two with a 3 centre stratification should mean, at worst, an imbalance of 3 participants however, there was an imbalance of 12. Letter written to Journal and authors responded acknowledging that imbalances should not have occurred. . [**However, given the realities of a complex multisite trial, perfection is rarely achieved. A combination of technical and human errors accounts for the imbalance (e.g., the laptop froze during randomization, the server went down temporarily, research assistants inadvertently practiced on a live site, and the participants went to the wrong session). To address this concern, we reassigned the 10 “in-error” participants to their original randomly assigned groups and found no less benefit of the resistance program in preventing completed rapes (relative risk reduction, 48.1% vs. 46.3%)**]. |
| **Rhodes, 2015 JAMA**After the individual has consented to participate in the study, they are ready to be enrolled and randomized to a treatment group. The Project Coordinator prepared opaque envelopes that are indistinguishable from each other and thick enough so that their contents are not legible from the outside. Research Assistant should return to the project office and draw the next sequential envelope from the file, beginning with #1001 for the first subject. | Use of envelopes increases risk of bias by advanced opening of envelopes. |
| **Chagpar 2015, New England Journal of Medicine**After written informed consent was obtained, patients were enrolled in the study, with stratificationinto one of two groups: patients with stage 0, I, or II cancer and those with stage IIIcancer. In each stratum, patients were randomly assigned in a 1:1 ratio to having either additional circumferential cavity shave margins resected (shave group) or no further tissue removed (no-shave group). Sealed randomization envelopes were assigned on the basis of a randomization list generated a priori at the Yale Center for Analytical Sciences. Study personnelwere unaware of the study-group assignments. The sealed randomization envelopes were opened intraoperatively after the surgeon completed the partial mastectomy. | Use of envelopes increases risk of bias by advanced opening of envelopes. |

\*Both trials were conducted at the same time by the same authors.

\*\*Originally unclear but after email correspondence became inadequate.

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