Epidemiology series

Allocation concealment in randomised trials: defending against deciphering

Kenneth F Schulz, David A Grimes

Proper randomisation rests on adequate allocation concealment. An allocation concealment process keeps clinicians and participants unaware of upcoming assignments. Without it, even properly developed random allocation sequences can be subverted. Within this concealment process, the crucial unbiased nature of randomised controlled trials collides with their most vexing implementation problems. Proper allocation concealment frequently frustrates clinical inclinations, which annoys those who do the trials. Randomised controlled trials are anathema to clinicians. Many involved with trials will be tempted to decipher assignments, which subverts randomisation. For some implementing a trial, deciphering the allocation scheme might frequently become too great an intellectual challenge to resist. Whether their motives indicate innocent or pernicious intents, such tampering undermines the validity of a trial. Indeed, inadequate allocation concealment leads to exaggerated estimates of treatment effect, on average, but with scope for bias in either direction. Trial investigators will be crafty in any potential efforts to decipher the allocation sequence, so trial designers must be just as clever in their design efforts to prevent deciphering. Investigators must effectively immunise trials against selection and confounding biases with proper allocation concealment. Furthermore, investigators should report baseline comparisons on important prognostic variables. Hypothesis tests of baseline characteristics, however, are superfluous and could be harmful if they lead investigators to suppress reporting any baseline imbalances.

> "The reason that the Medical Research Council's controlled trial of streptomycin for pulmonary tuberculosis should be regarded as a landmark is thus not, as is often suggested, because random number tables were used to generate the allocation schedule . . . Rather it is because of the clearly described precautions that were taken to conceal the allocation schedule from those involved in entering patients."[1]

Generation of an unpredictable randomised allocation sequence represents the first crucial element of randomisation in a randomised controlled trial.[2] Implementation of the sequence, while concealing it at least until patients have been assigned to their groups (allocation concealment), is the important second element,[3,4] without which, randomisation collapses in a trial.

As a direct consequence of randomisation, the first table in most reports of randomised controlled trials describes the baseline characteristics of the comparison groups.[5] Researchers should describe their trial population and provide baseline comparisons of their groups so that readers can assess their comparability.[5] In this article, we focus on proper approaches to allocation concealment and to reporting of baseline characteristics.

Allocation concealment

Researchers have many misconceptions with respect to allocation concealment. Proper allocation concealment secures strict implementation of a random allocation sequence without foreknowledge of treatment assignments. Allocation concealment refers to the technique used to implement the sequence,[4] not to generate it. Nevertheless, some people discuss allocation concealment with digressions into flipping coins or use of random number tables. Those digressions amount to methodological non-sequiturs; allocation concealment is distinct from sequence generation. Furthermore, some investigators confuse allocation concealment with blinding of treatments.[3,4,6]

Without adequate allocation concealment, even random, unpredictable assignment sequences can be undermined.[4,7,8] Knowledge of the next assignment could lead to the exclusion of certain patients based on their prognosis because they would have been allocated to the perceived inappropriate group. Moreover, knowledge of the next assignment could lead to direction of some participants to perceived proper groups, which can easily be accomplished by delaying a participant's entry into the trial until the next appropriate allocation appears. Avoidance of such bias depends on the prevention of foreknowledge of treatment assignment. Allocation concealment shields those who admit participants to a trial from knowing the upcoming assignments. The decision to accept or reject a participant should be made, and informed consent should be obtained, in ignorance of the upcoming assignment.[9]

Importance of allocation concealment

Results of four empirical investigations[4,10–12] have shown that trials that used inadequate or unclear allocation concealment, compared with those that used adequate concealment, yielded up to 40% larger estimates of effect. The badly done trials tended to exaggerate treatment effects. Moreover, the worst concealed trials yielded greater heterogeneity in results—ie, the results fluctuated extensively above and below the estimates from better studies.[4] These findings provide empirical evidence that inadequate allocation concealment allows bias to seep into trials.

Indeed, having a randomised (unpredictable) sequence should make little difference without adequate allocation

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Family Health International, PO Box 13950, Research Triangle Park, NC 27709, USA (K F Schulz PhD, D A Grimes MD)

Correspondence to: Dr Kenneth F Schulz
(e-mail: KSchulz@fhi.org)

concealment. Assume that investigators generate an adequate allocation sequence with a random number table. They then, however, post that sequence on a bulletin board, so that anyone involved in the trial could see the upcoming assignments. Similarly, the allocation sequence could be implemented through placing method indicator cards in translucent envelopes. This inadequate allocation concealment process could be deciphered by simply holding the envelopes to a bright light (figure). With both the bulletin board and the envelopes, those responsible for admitting participants could detect the upcoming treatment assignments and then channel individuals with a better prognosis to the experimental group and those with a poorer prognosis to the control group, or vice versa. Bias could easily be introduced, despite an adequate randomised sequence.[7]

Deciphering the allocation concealment scheme

Researchers should, therefore, ensure both adequate sequence generation and adequate allocation concealment in randomisation schemes.[3,4,13] A mistake in either could compromise randomisation, resulting in incorrect results. For example, results of a trial could reveal a large treatment effect that only reflects a biased allocation procedure, or they could reveal no effect when in reality a harmful one prevails. Moreover, the results of such a trial can be more damaging than similar results from an explicitly observational research study.[14] Biases are usually assumed and acknowledged in observational studies, and the statistical analysis and eventual interpretation attempt to take those biases into account. Conversely, studies labelled as randomised are frequently assumed to be free of bias, and commonly inadequate reporting masks the deficiencies they might have.[3,13]

Consequently, the credibility of randomised controlled trials lends support to faster and greater changes in clinical or preventive management, which, if based on a compromised study, squanders scarce health resources, or even worse, harms peoples' health. Thus, the well-deserved credibility of randomised controlled trials produces an indirect liability. Wrong judgments emanate easily from improperly randomised trials.

Personal accounts of deciphering

Findings of empirical investigations[4,10–12] suggest that investigators sometime undermine randomisation, though they rarely document such subversions. Nevertheless, when investigators responded anonymously to queries during epidemiological workshops, many did relate instances in which allocation schemes had been sabotaged.[7]

The individual accounts of such instances describe a range of simple to intricate operations.[7] Most allocation concealment schemes were deciphered by investigators simply because the methods were inadequate. Investigators admitted, for instance, altering enrolment or allocations to particular study groups after decoding future assignments, which were either posted on a bulletin board or visible through translucent envelopes held up to bright lights. Some also related opening unsealed assignment envelopes, sensing the differential weight of envelopes, or simply opening unnumbered envelopes until they found a desired treatment.

Investigators had a harder time deciphering the better allocation concealment schemes.[7] Nevertheless, eventually someone described circumventing virtually every type of scheme. For example, some physicians took sequentially numbered, opaque, sealed envelopes to the hot light (an intense incandescent bulb) in the radiology department for deciphering of assignments. In studies using central randomisation, trial investigators related ringing the central number and asking for the next several assignments all at once; they received them in at least a couple of circumstances. In trials with sequentially numbered drug containers, someone described deciphering assignments based on the appearance of the container labels. Another had stopped trying to decipher a drug container scheme until she saw an attending physician, late at night, ransacking the office files of the principal investigator for the allocation list. Suggesting her methodological naïveté and innocence, she first thought of the attending physician's cleverness and not of the probability that such action would bias the trial.

Although investigators theoretically understand the need for unbiased research, they sometimes fail to maintain impartiality once they are involved in a trial. Researchers might want certain patients to benefit from one of the treatments, or the trial results to confirm their beliefs. Thus, certain trial procedures in properly done randomised controlled trials frustrate clinical inclinations, which annoys those doing the trial.[7,15,16]

Some scientists aim to deliberately sabotage their results. However, many attempts at decoding the randomisation sequence simply indicate an absence of knowledge of the scientific ramifications of such actions. Furthermore, for some, the deciphering of the allocation scheme might frequently become too great an intellectual challenge to resist. As Oscar Wilde wrote, "The only way to get rid of temptation is to yield to it." Whether their motives are innocent or not, however, such tampering undermines the validity of a trial. Investigators must recognise the inquisitiveness of human nature and institute methodological safeguards. Proper allocation concealment will deter subversion, in effect, immunising trials against selection and confounding biases.[7,15,16]

To develop a proper allocation scheme takes time, effort, and thought. Investigators cannot simply delegate this task without thoroughly examining the final product. Trial investigators will be crafty in any potential efforts to decipher the allocation sequence, so trial designers must be just as clever in their design efforts to prevent deciphering.

What to look for with allocation concealment

Researchers consider certain approaches to allocation concealment as adequate: sequentially numbered, opaque, sealed envelopes (SNOSE); pharmacy controlled; numbered or coded containers; central randomisation—eg, by telephone to a trials office—or other method whose description contained elements convincing of concealment—eg, a secure computer-assisted method.[3,4,17] These criteria establish minimum methodological standards, yet they are met by only about a quarter of trials.[3,17] Consequently, in assessment of allocation concealment from published reports, readers will be fortunate to find such standards reasonably met (panel 1).[18–23] Realistically, however, those minimum standards should be exceeded. If researchers provide descriptions that incorporate not only the minimum standards, but also elements of more rigorous standards, readers can have more confidence that selection and confounding biases have been averted (panel 2).

Methods that use envelopes are more susceptible to manipulation through human ingenuity than other approaches, and are therefore considered a less than ideal method of concealment.[24] If investigators use envelopes, they should diligently develop and monitor the allocation process to preserve concealment. In addition to use of sequentially numbered, opaque, sealed envelopes, they should ensure that the envelopes are numbered in advance, opened sequentially, and only after the participant's name and other details are written on the appropriate envelope.[25] We also recommend use of pressure sensitive or carbon paper inside the envelope, which transfers such information to the assigned allocation and thus creates a valuable audit trail. Cardboard or aluminum foil placed inside the envelope further inhibits detection of assignments via hot lights.

Pharmacies can also engender both allocation-concealment and sequence-generation difficulties. Although reports in which the assignment was made by the pharmacy have generally been classified as having used an acceptable allocation concealment mechanism,[3,4,17] compliance of pharmacists with proper randomisation methods in these trials is unknown. The precautions they took should have been reported. We are aware of instances in which pharmacists have violated assignment schedules.[7] For instance, one large pharmacy charged a project US$150 per participant for randomisation. During the course of the trial, over a weekend, the pharmacy ran out of one of the two drugs being compared, and therefore allocated the other drug to all newly enrolled participants to avoid slowing recruitment. We are aware of another pharmacy that randomised patients by alternate assignment. Investigators should not assume that pharmacists, and others involved in their trials, know about the methods of randomised controlled trials. Investigators must ensure that their research partners adhere to proper trial procedures. Beyond the minimum criteria, readers would gain additional confidence if investigators indicate that they instructed or checked the allocation mechanism of the pharmacy.

The use of sequentially numbered containers prevents foreknowledge of treatment assignment, but only if investigators take proper precautions. Beyond the minimum criteria, authors of trial reports should specify further details of the methods. Assurances that all of the

Panel 1: **Descriptions of allocation concealment**

" . . . that combined coded numbers with drug allocation. Each block of ten numbers was transmitted from the central office to a person who acted as the randomisation authority in each centre. This individual (a pharmacist or a nurse not involved in care of the trial patients and independent of the site investigator) was responsible for allocation, preparation, and accounting of trial infusion. The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h. The nurse infused it into the patient at the appropriate rate. The randomisation schedule was thus concealed from all care providers, ward physicians, and other research personnel."[18]

". . . concealed in sequentially numbered, sealed, opaque envelopes, and kept by the hospital pharmacist of the two centres."[19]

"Treatments were centrally assigned on telephone verification of the correctness of inclusion criteria . . ."[20]

"Glenfield Hospital Pharmacy Department did the randomisation, distributed the study agents, and held the trial codes, which were disclosed after the study."[21]

"The various placebo and treatment blocks were then issued with a medication number and assigned to consecutive patients in a sequential order. Two copies of the randomisation list were prepared: one was used by the packaging department, . . . supplied in blister packs containing 20 capsules for morning and evening administration over 10 days. These blister packs were supplied in labeled boxes—ie, one box for each patient and each dose."[22]

"Individuals were randomised by a computer-generated list, which was maintained centrally so no centre knew the treatment allocation of any patient. Marked capsule containers were designated for each patient, with additional containers being available should an increase to 15 mg or 20 mg sibutramine or placebo be prescribed by the centre's physician."[23]

Panel 2: **Minimum and expanded criteria for adequate allocation concealment schemes**

Minimum description of adequate allocation concealment scheme	**Additional descriptive elements that provide greater assurance of allocation concealment**
Sequentially numbered, opaque, sealed envelopes (SNOSE)	Envelopes are opened sequentially only after participant details are written on the envelope. Pressure-sensitive or carbon paper inside the envelope transfers that information to the assignment card (creates an audit trail). Cardboard or aluminum foil inside the envelope renders the envelope impermeable to intense light.
Sequentially numbered containers	All of the containers were tamper-proof, equal in weight, and similar in appearance.
Pharmacy controlled	Indications that the researchers developed, or at least validated, a proper randomisation scheme for the pharmacy. Indications that the researchers instructed the pharmacy in proper allocation concealment.
Central randomisation	The mechanism for contact—eg, telephone, fax, or e-mail—the stringent procedures to ensure enrolment before randomisation, and the thorough training for those individuals staffing the central randomisation office.

containers were tamper-proof, equal in weight, and similar in appearance, and that some audit trail had been established (such as writing the names of participants on the empty bottles or containers) would help readers to assess whether randomisation was likely to have been concealed successfully. Similarly, although central randomisation continues to be an excellent allocation concealment approach, effective trial procedures need to be established and followed. Researchers should at least specify the mechanism for contact—eg, telephone, fax, or e-mail—the stringent procedures to ensure enrolment prior to randomisation, and the thorough training of individuals at the central randomisation office. All these details should be addressed when doing a trial and when writing a trial report.[7,13]

Other methods might suffice for adequate allocation concealment. Readers should look for descriptions that contain elements convincing of concealment. For example, a secure computer-assisted method might enable allocation concealment by preservation of assignments until enrolment is assured and confirmed. Indeed, automated assignment systems are likely to become more common.[26,27] However, a simple computer system that merely stores assignments or naïvely shields assignments could turn out to be as transparent as tacking a randomisation list to a bulletin board. In describing an allocation concealment mechanism, investigators should display knowledge of the rationale behind allocation concealment and how their method met the standards.

Researchers frequently fail to report even the barest of descriptions of allocation concealment, preventing readers from assessing randomised controlled trials. The mechanism used to allocate interventions was omitted in reports of 93% of trials in dermatology,[28] 89% of trials in rheumatoid arthritis,[29] 48% of trials in obstetrics and gynecology journals,[3] and 45% of trials in general medical journals.[17] Fortunately, the situation is improving, since more medical journals are adopting reporting standards for randomised controlled trials.[5,13,30] Moreover, with that reporting impetus, more investigators might design and do sound trials.

Baseline comparisons

Although randomisation eliminates systematic bias, it does not necessarily produce perfectly balanced groups with respect to prognostic factors. Differences due to chance remain in the intervention groups—ie, chance maldistribution. Statistical tests, however, account for these chance differences. The process of randomisation underlies significance testing and is independent of prognostic factors, known and unknown.[31]

Nevertheless, researchers should present distributions of baseline characteristics by treatment group in a table (table). Such information describes the hypothetical population from which their trial arose and allows readers to see the possibilities of generalisation to other populations.[32] Furthermore, it allows physicians to infer the results to particular patients.[5]

	Antibiotic group (n=116)	Placebo group (n=129)
Characteristic		
Age (mean [SD]) (years)	30·2 (5·2)	31·1 (5·9)
Weight (median [25th, 75th centiles]) (kg)	141 (122, 181)	144 (123, 188)
Nulliparous (number, %)	62 (53%)	63 (49%)
Previous pelvic inflammatory disease (number, %)	24 (21%)	28 (22%)

Example of a reasonably reported table of baseline characteristics

A table of baseline characteristics also allows readers to compare the trial groups at baseline on important demographic and clinical characteristics. The common, inappropriate use of hypothesis tests—eg, p values in the tables—to compare characteristics concerns us, however.[3,17,33,34] Such tests assess the probability that differences observed could have happened by chance. In properly randomised trials, however, any observed differences have, by definition, occurred by chance. "Such a procedure is clearly absurd," as Altman states.[34]

Hypothesis tests on baseline characteristics might not only be unnecessary but also harmful. Researchers who use hypothesis tests to compare baseline characteristics report fewer significant results than expected by chance.[3,17] One plausible explanation for this discrepancy is that some investigators might have decided not to report significant differences, believing that by witholding that information they would increase the credibility of their reports. Not only are hypothesis tests superfluous, but they can be harmful if they indirectly lead investigators to suppress reporting baseline imbalances.

What to look for with baseline characteristics

Investigators should report baseline comparisons on important prognostic variables. Readers should look for comparisons based on consideration of the prognostic strength of the variables measured and the magnitude of any chance imbalances that have occurred, rather than statistical significance tests at baseline.[34] A table provides an efficient format of presenting baseline characteristics (table). Researchers should present continuous variables, such as age and weight, with an average and a measure of variability; usually a mean and standard deviation. If the data distribute asymmetrically, however, a median and a percentile range—ie, interquartile range—would provide better descriptions. Variability should not be described by standard errors and confidence intervals, since they are inferential rather than descriptive statistics.[5] Numbers and proportions should be reported for categorical variables.[5]

In the analysis, the statistical tests on the outcomes account for any chance imbalances. Nevertheless, controlling for chance imbalances, if properly planned and done, might produce a more precise result.[35] Researchers should present any adjusted analyses and describe how and why they decided to adjust for certain covariates.

Conclusion

Proper randomisation remains the only way to avoid selection and confounding biases. The crucial unbiased nature of randomised controlled trials paradoxically coincides with their most vexing implementation problems. Randomised controlled trials antagonise human beings by frustrating their clinical inclinations. Thus, many involved with trials will be tempted to undermine randomisation, if afforded the opportunity to decipher assignments. To minimise the effect of this human tendency, trialists must devote meticulous attention to concealment of allocation schemes. Proper randomisation hinges on adequate allocation concealment.

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