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EBN notebook

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Assessing allocation concealment and blinding in randomised controlled trials: why bother?

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The EBN users' guide in the previous issue of *Evidence-Based Nursing* outlined the primary and secondary questions for evaluating studies of healthcare interventions. One of the primary questions for assessing the validity of a study's findings is whether the assignment of patients to treatments was randomised and whether randomisation was concealed. One of the secondary questions is whether patients, clinicians, outcome assessors, and data analysts were unaware of (blinded to or masked from) patient allocation. Beginning with the October 1999 issue of *Evidence-Based Nursing*, allocation concealment and blinding have been given more attention. The "design" section of abstracts of randomised trials now includes a statement of whether randomisation was concealed from those responsible for entering patients into trials, and who was blinded to treatment allocation during the trials. These additional specifications provide readers with more information to judge the internal validity of trials. In this editorial, the background and rationale for these decisions are addressed.

Allocation concealment

Random allocation to intervention groups remains the only method of ensuring that the groups being compared are on an equivalent footing at study outset, thus eliminating selection and confounding biases. This has allowed randomised controlled trials (RCTs) to play a key part in advancing healthcare practice.

The success of randomisation depends on 2 interrelated processes.[1,2] The first entails generating a sequence by which the participants in a trial are allocated to intervention groups. To ensure unpredictability of that allocation sequence, investigators should generate it by a random process (eg, computer generated numbers, random number tables, or coin flipping). The second process, *allocation concealment*, shields those involved in a trial from knowing upcoming assignments in advance.[3,4] Without this protection, investigators have been known to change who gets the next assignment, making the comparison groups less equivalent.[5,6]

Suppose, for example, that an investigator creates an adequate allocation sequence using a random number table. However, the investigator then affixes the list of that sequence to a bulletin board, with no allocation concealment. Those responsible for admitting participants could ascertain the upcoming treatment allocations and then route participants with better prognoses to the experimental group and those with poorer prognoses to the control group, or vice versa. Bias would result. Inadequate allocation concealment also exists, for example, when assignment to groups depends on whether a participant's hospital number is odd or even, or depends on translucent envelopes that allow discernment of assignments when held up to a light bulb. Strategies to conceal allocation include calling a central, coordinating office for each patient assignment at the time that the patient presents for study inclusion; using sequentially numbered, opaque, sealed envelopes; and using numbered bottles or containers. In this issue of *Evidence-Based Nursing*, a study by Richter *et al* evaluates the effectiveness of on demand β_2-agonist inhalation in reducing the number of asthma episodes in patients with moderate to severe asthma.[7] The investigators ensured unpredictability of the allocation sequence by using a computerised random number generation process. To shield those responsible for entering patients into the trial from knowing upcoming assignments, they used sequentially numbered, opaque, sealed envelopes. Unfortunately, their article neglected to state the sequentially numbered aspect. On average, such articles yield exaggerated results, as discussed below.[3] Thus, their original report creates a false impression of poor allocation concealment. The authors confirmed when contacted, however, that they used numbered envelopes. Each envelope contained the group assignment for one patient.

Recent studies have shown that poorly designed RCTs and poorly reported RCTs yield biased results. For example, in a study of 250 controlled trials from 33 meta-analyses in pregnancy and childbirth, investigators found that alleged RCTs with inadequate and unclear allocation concealment yielded larger estimates of treatment effects (on average 41% and 33%, respectively) than trials in which authors reported adequate concealment.[3] Investigators found similar results for trials in digestive diseases, circulatory diseases, mental health, and stroke.[4] Trials that used inadequate or unclear allocation concealment yielded, on average, 37% larger estimates of effect than trials that used adequate concealment. These exaggerated estimates of treatment effects reveal meaningful levels of bias. If a study were designed to detect an improvement in quality of life of 25% or 50% from a particular treatment, biases of 30% to 40% would overwhelm estimates of the treatment effect. The elimination of bias is crucial in trials designed to detect moderate effects.

In the "design" section of abstracts of RCTs in *Evidence-Based Nursing*, allocation concealment is now described as follows:

- Allocation concealed: deemed to have taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (ie, central randomisation; sequentially numbered, opaque, sealed envelopes; numbered or coded bottles or containers; drugs prepared by the pharmacy; or other descriptions that contain elements convincing of concealment).
- Allocation not concealed: deemed to have not taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (ie, no concealment procedure was undertaken, sealed envelopes that were not opaque or that were not sequentially numbered, or other descriptions that contained elements not convincing of concealment).
- Unclear allocation concealment: the authors did not report or provide a description of an allocation concealment approach that allowed for the classification as concealed or not concealed.

Allocation concealment should not be confused with blinding. Allocation concealment concentrates on preventing selection and confounding biases, safeguards the assignment sequence *before and until* allocation, and can *always* be successfully implemented.[1] By comparison, blinding concen-

trates on preventing study participants and personnel from determining the group to which participants have been assigned (which leads to ascertainment bias), safeguards the sequence *after* allocation, and cannot always be implemented.[1 9]

Blinding

Blinding or *masking* involves keeping patients, clinicians, outcome assessors, and/or data analysts unaware of patient allocation to avoid bias. For example, if unblinded, patients may have a heightened sensitivity to the good (or bad) effects of the treatment, clinicians may unwittingly alter the way they provide care or look for good or adverse outcomes, outcome assessors may distort outcome measurement, and data analysts may alter their approach to analysing the data. Ideally, although not usually possible in studies evaluating nursing interventions, all 4 groups are blinded. In the study by Richter *et al* described above, 2 of these groups were blinded, the outcome assessors and the data analysts. The authors explained that blinding of patients was not possible because the patients could easily identify the (side) effects of β_2-agonists. There was no mention of clinician blinding.

Double blinding (variably but usually defined as blinding patients, clinicians, and outcome assessors) also appears to reduce bias. Trials that were not double blinded yielded larger estimates of treatment effect than trials in which authors reported double blinding (odds ratios exaggerated, on average, by 17%).[5] Another recent analysis similarly indicated the importance of double blinding.[10] However, although double blinding seems to prevent bias, its effect appears weaker than that of allocation concealment. Indeed, Moher *et al* found that double blinding had little influence on estimates of effect.[8] In the "design" section of abstracts of RCTs in *Evidence-Based Nursing*, the study is now identified as *blinded*, with specification of who was blinded; *unblinded*, if all parties were aware of patients' group assignments; or *blinded (unclear)* if the authors did not report or provide an indication of who was aware or unaware of patients' group assignments.

Reporting of methods

Investigators must not only minimise bias but must also communicate those efforts to the reader. Readers should not have to assume or guess which methods were used. Yet assessments of the reporting quality of published trials have consistently found major flaws.[3 11-17] Only 9% of trials in specialist journals and 15% in general journals reported both an adequate method of generating random sequences and an adequate method of allocation concealment.[3 11 18] Of trials reported as double blind, only 45% described similarity of the treatment and control regimens, and only 26% provided information on the protection of the allocation schedule.[19] Most reports simply provide no information on methods. When reports of studies abstracted for *Evidence-Based Nursing* do not include information about allocation concealment or blinding, the authors are asked to provide this information.

With so little relevant information, many readers resort to inappropriate markers of trial quality. Two noteworthy examples highlight this concern. Firstly, many designate a trial as high quality if it is "double blind," as if double blinding is the essential requirement of an RCT. Although double blinding can reflect good methods, it is not the sole criterion of quality. Adequate allocation concealment actually appears to be the more important indicator. Moreover, many trials cannot be double blinded. Those trials must be judged on other merits and not on an inapplicable standard based on double blinding. To further complicate matters, a study recently found that the term "double blind" was interpreted differently both by readers and by experts. Surveys of physicians and review of recent textbooks including definitions for blinding revealed numerous unique interpretations for the term; for example, some thought it meant that the patients and clinicians were blinded, whereas others thought that the patients and outcome assessors were blinded. This has led to the recommendation that the terms single, double, and triple blinded be abandoned and replaced with descriptions specifically stating *which* of the groups were unaware of allocation.[20]

Secondly, some assume that a good quality trial contains arms of equal size, whereas a poor quality trial contains unequal sizes. This standard has marginal value only when the investigators used a restricted randomisation generation scheme that aimed for equality. Otherwise, exactly equal numbers in treatment groups in a simple randomised trial may mean that some process *other* than randomisation was used (eg, allocation of every second patient to the intervention group).

Although RCT reporting remains weak, it is improving. Methodologists, editors, and clinicians addressed the prevailing flaws in reporting by publishing the Consolidated Standards of Reporting Trials (CONSORT) statement.[21] Currently, 48 journals have adopted the standards, including such high profile healthcare journals as *JAMA*, *BMJ*, *Pediatrics*, and *Archives of Internal Medicine*. These journals were 4 of the highest contributors of articles to *Evidence-Based Nursing* in 1998 and 1999.[22] Sadly, no nursing journals have yet adopted the standards. Even with these improvements, readers of RCTs should be wary of the information provided in many current trial reports.

Summary

As users of RCT results, we must understand the potential for humans to interject bias. By describing assessments of allocation concealment and blinding, abstracts included in *Evidence-Based Nursing* will help readers to discern those trials that have made superior efforts to minimise bias. Judging the quality of allocation concealment and blinding reflects current empirical research and reflects the commitment of the editors of this journal to apply the principles of evidence-based practice to reporting of study findings.

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1 Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995;274:1456–8.

2 Schulz KF. Randomized trials, human nature, and reporting guidelines. *Lancet* 1996;348:596–8.

3 Schulz KF, Chalmers I, Grimes DA, *et al*. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. *JAMA* 1994;272:125–8.

4 Chalmers TC, Levin H, Sacks HS, *et al*. Meta-analysis of clinical trials as a scientific discipline. I: control of bias and comparison with large co-operative trials. *Stat Med* 1987;6:315–28.

5 Schulz KF, Chalmers I, Hayes RJ, *et al*. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.

6 Pocock SJ. Statistical aspects of clinical trial design. *Statistician* 1982;31:1–18.

7 Richter B, Bender R, Berger M. Effects of on-demand β_2-agonist inhalation in moderate-to-severe asthma. A randomized controlled trial. *J Intern Med* 2000;247:657–66.

8 Moher D, Pham B, Jones A, *et al*. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609–13.

9 Schulz KF. Unbiased research and the human spirit: the challenges of randomized controlled trials. *CMAJ* 1995;153:783–6.

3

10 Khan KS, Daya S, Collins JA, *et al.* Empirical evidence of bias in infertility research: overestimation of treatment effect in crossover trials using pregnancy as the outcome measure. *Fertil Steril* 1996;**65**:939–45.
11 Altman DG, Doré CJ. Randomization and baseline comparisons in clinical trials. *Lancet* 1990;**335**:149–53.
12 Moher D, Fortin P, Jadad AR, *et al.* Completeness of reporting of trials published in languages other than English: implications for the conduct and reporting of systematic reviews. *Lancet* 1996;**347**:363–6.
13 Williams DH, Davis CE. Reporting of assignment methods in clinical trials. *Control Clin Trials* 1994;**15**:294–8.
14 Sonis J, Joines J. The quality of clinical trials published in *The Journal of Family Practice*, 1974–1991. *J Fam Pract* 1994;**39**:225–35.
15 Mosteller F, Gilbert JP, McPeek B. Reporting standards and research strategies for controlled trials: agenda for the editor. *Control Clin Trials* 1980;**1**:37–58.
16 DerSimonian R, Charette LJ, McPeek B, *et al.* Reporting on methods in clinical trials. *N Engl J Med* 1982;**306**:1332–7.
17 Tyson JE, Furzan JA, Reisch JS, *et al.* An evaluation of the quality of therapeutic studies in perinatal medicine. *J Pediatr* 1983;**102**:10–13.
18 Schulz KF, Chalmers I, Altman DG, *et al.* The methodologic quality of randomization as assessed from reports of trials in specialist and general medical journals. *Online J Curr Clin Trials* [serial online] 1995 August 26;4(Doc No 197):[81 paragraphs].
19 Schulz KF, Grimes DA, Altman DG, *et al.* Blinding and exclusions after allocation in randomised controlled trials: survey of published parallel group trials in obstetrics and gynaecology. *BMJ* 1996;**312**:742–4.
20 Devereaux PJ, Manns BJ, Ghali WA *et al.* In the dark: physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. *JAMA* in press
21 Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**:637–9.
22 DiCenso A, Cullum N, Ciliska D, *et al. Evidence-Based Nursing*: past, present, and future [editorial]. *Evidence-Based Nursing* 2000;**3**:7–8.

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