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

The scientific community's quest for unbiased research received a strong boost from a recent policy amendment on randomised controlled trials (RCTs) in this journal. Henceforth, the status of allocation concealment will be clearly indicated in the abstracts along with that of blinding, so readers will have additional information by which to judge the internal validity of trials. In this editorial, I address the background of and rationale for these enhancements.

Background

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 technique has allowed RCTs to play a key role in advancing medical science.

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 the unpredictability of that allocation sequence, investigators should generate it by a random process. The second process, allocation concealment, shields those involved in a trial from knowing upcoming assignments. Without this protection, investigators and patients have been known to change who gets the next assignment, making the comparison groups less equivalent.³⁻⁶

For example, suppose 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 on translucent envelopes that allow discernment of assignments when held up to a light bulb.

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.^{1,2} Blinding concentrates on preventing study personnel and participants 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.¹⁻⁷

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 the methods used. Yet assessments of the reporting quality of published trials have consistently found major flaws.^{3,8-14} Only 9% of trials in the specialist journals and

15% in the general journals reported both an adequate method of generating random sequences and an adequate method of allocation concealment.^{3,8,15} 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.¹⁶ Most reports simply provide no information on methods.

With so little relevant information, many of us resort to inappropriate markers of trial quality. 2 noteworthy examples are described here. First, many designate a trial as high quality if it is "double blind", as if double blinding is the sine qua non of an RCT. Although double blinding can reflect good methods, it is not the sole criterion of quality. As I shall discuss later, 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.

Second, some assume that a good-quality trial contains groups of equal size, while a poor-quality trial contains groups of unequal size. That standard applies only when the investigators use a restricted randomisation generation scheme that aims for equality. A simple randomisation method will seldom yield equal sample sizes. In fact, equal numbers in treatment groups may mean that some process other than randomisation was used, for example, allocation of every second patient to the intervention group or the use of odd and even birth dates or chart numbers as a way to assign participants to study groups.

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.¹⁷ Currently, more than 70 journals have adopted the standards, including such high-profile general medical journals as *JAMA*, the *Lancet*, *BMJ*, and *Annals of Internal Medicine*. Yet, even with improvement, readers of RCTs should be wary of the information provided in many current trial reports.

Empirical evidence of bias

Recent studies have shown that poor-quality 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 (41% and 33%, respectively, on average) than trials in which authors reported adequate concealment.⁵ Investigators found similar results for trials in digestive diseases, circulatory diseases, mental health, and stroke.¹⁸ Those trials that used inadequate or unclear allocation concealment yielded 37% larger estimates of effect, on average, than those that used adequate concealment.

These exaggerated estimates of treatment effects reveal meaningful levels of bias. If a study is designed to detect a

decrease in mortality 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.

Double blinding also appears to reduce bias. Trials that were not double blinded yielded larger estimates of treatment effects than did trials in which authors reported double blinding (odds ratios exaggerated, on average, by 17%).⁵ Another recent analysis has also noted the importance of double blinding.¹⁹ However, although double blinding appears to prevent bias, its effect appears weaker than that of allocation concealment. Indeed, Moher and colleagues found little effect from double blinding.¹⁸

Conclusions

As users of RCT results, we must understand the potential for humans to interject bias. By including assessments of allocation concealment and double blinding, abstracts in this journal 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 medicine to the practice of reporting.

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Incorporating allocation concealment and blinding in randomised controlled trials

While we are happy to take credit for incorporating more information on blinding and concealment in our abstracts, the credit for stimulating us to do so belongs elsewhere. First, Ken Schulz and others have shown us that randomisation, blinding, and concealment of allocation make a difference to the accuracy of trial reports. Second, Phillip Devereaux and others have taken us to task for failing to report these important features of clinical trials. Readers will find that abstracts of trials now include whether the randomisation was concealed from those responsible for entering patients into trials and who was blinded to treatment allocation during the trial. This information will be provided under the "Design" heading in abstracts whenever it is possible to obtain it from the study report or, failing that, directly from the investigators.

Unfortunately, our experience to date shows that it is not always possible to acquire an unequivocal answer from authors about blinding or allocation concealment. For example, the trial may be billed as "double blind," but the regimen appears to have adverse effects that might reveal to patients or investigators who was taking it; in such cases authors may not check to see if the blinding is maintained. Or the investigator indicates that sealed envelopes were used to conceal randomisation, but whether the envelopes were opaque is not indicated. If, in our judgment, there is reason to suspect that blinding or concealment was not secure, we will indicate that by rating the appropriate feature as "unclear". In doing so, we do not mean to offend investigators who have done their best to protect their trials from bias; rather, we wish to protect readers from us, the editors, conveying a sense of false security about studies for which we remain uncertain about the method used for concealment or blinding.

The definitions that we will use for the categories of allocation concealment are as follows:

Allocation concealed: the authors were deemed to have taken adequate measures to conceal allocation to study group

assignments from those responsible for assessing patients for entry in the trial (eg, central randomisation; numbered, opaque, sealed envelopes; sealed envelopes from a closed bag; numbered or coded bottles or containers; drugs prepared by the pharmacy; or other descriptions that contain elements convincing of concealment).

Allocation not concealed: the authors were deemed not to have taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (eg, no concealment procedure, sealed envelopes that were not opaque, or other descriptions that contain elements not convincing of concealment).

Unclear allocation concealment: the authors did not report or provide us with a description of an allocation concealment approach that allowed for classification as concealed or not concealed.

The definitions that we will use for the categories of blinding are as follows:

Blinded: any or all of the clinicians, patients or participants, outcome assessors, or statisticians were unaware of who received which study intervention. If "initially" is indicated (eg, blinded [patients and outcome assessor initially]), the code was broken during the trial, for instance, because of adverse effects.

Blinded (unclear): the authors did not report or provide us with an indication of who, if anyone, was unaware of who received which study intervention.

Unblinded: all participants in the trial (clinicians, patients or participants, outcome assessors, and statisticians) were aware of who received which study intervention.

These definitions have been added to the glossary, which can be found in each issue of the journal.

R BRIAN HAYNES, MD, PhD
Editor

Corrections

In the January/February 1999 issue of *Evidence-Based Medicine*, 2 errors were detected in the abstract for the article by Gloaguen *et al.*¹ In the main results section of the abstract, we indicate that there was no significant heterogeneity in the results of studies comparing CT *v* other therapies when in fact there was. Furthermore, we indicate that there was significant heterogeneity in the results of studies comparing CT *v* behaviour therapy when in fact there was not.

1 Review: cognitive therapy is beneficial and equivalent to behaviour therapy and antidepressants for mild-to-moderate depression [abstract]. *Evidence-Based Medicine* 1999 Jan/Feb;4:20. Abstract of: Gloaguen V, Cottraux J, Cucherat M, *et al.* A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord* 1998 Apr;49:59-72.

The editors regret the omission of Dr Bel Barker as a co-author of a recent commentary.¹ We apologise to Drs Barker and Garcia. The commentary authorship information should be as follows: Francisco A Garcia, MD, MPH; Bel Barker, MD; University of Arizona; Tucson, Arizona, USA.

1 Garcia FA, Barker B. Commentary on "A McCall-type culdeplasty was effective for preventing enteroceles after vaginal hysterectomy." *Evidence-Based Medicine* 1999 Nov/Dec;4:181. Comment on: Cruikshank SH, Kovac SR. Randomized comparison of three surgical methods used at the time of vaginal hysterectomy to prevent posterior enterocele. *Am J Obstet Gynecol* 1999;180:859-65.