ABC of Methodology

This is a new Section of *Epidemiologia e Psichiatria Sociale*, that will regularly cover methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. We hope that these articles will help develop a more critical attitude towards research findings published in the international literature and, additionally, will help promote the implementation of original research projects with higher standards in terms of design, conduct and reporting.

Corrado Barbui, *Section Editor* and Michele Tansella, *Editor* EPS

Allocation concealment and blinding in clinical trials

ANDREA CIPRIANI, MICHELA NOSÈ, CORRADO BARBUI

Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona, Italy

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Randomized controlled trials (RCTs) are considered the strongest research design to estimate the effects of health interventions. The Consolidated Statement of Reporting Trials (CONSORT) provides readers of RCTs with a list of criteria useful to assess trial validity (www.consort-statement.org). Together with randomisation, *blinding* and *allocation concealment* are among these criteria.

Randomization is a process that aims at producing groups that are similar in terms of both known and unknown prognostic factors (Altman & Bland, 1999). By generating two groups of subjects with similar characteristics, the randomization minimizes *confounding* (*confounding* is the bias that occurs when one group of subjects has certain features - known or unknown - that affect the relationship between the intervention and the outcome of interest). The process of randomization begins with the generation of a random allocation sequence. The sequence is used to randomly allocate patients to two (or more) treatment groups. This process is equivalent to tossing a coin, but in practice investigators typically use allocation sequences randomly generated by a computer software. Similar lists of random numbers can additionally be found in most statistics textbooks.

Address for correspondence: Dr. A. Cipriani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona (Italy).
Fax: +39-045-585.871
E-mail: andrea.cipriani@univr.it

The process of randomisation does not end until participants are actually assigned to their groups. So, randomization should be considered a series of events that includes, but is not limited to, the generation of a random allocation sequence. Another of these events is the concealment of *allocation*. It is a way to ensure that subjects, investigators and all other health care providers involved in the conduct of the study do not know to which group a subject will be allocated before the subject is entered into the study (that is do not have access to the random allocation sequence). In other words, *allocation concealment* refers to preventing the next assignment in the clinical trial from being known (point A in the Figure) (Schulz & Grimes, 2002).

Allocation concealment is different from *blinding* (or "masking"). In clinical trials *blinding* refers to the prevention of knowledge of treatment assignment after randomisation has been done. By contrast, *allocation concealment* refers to the prevention of knowledge of upcoming assignment from the randomisation sequence before the treatment is allocated. For these reasons, *allocation concealment* is part of the randomisation process and has always to be included in the design of an RCT. Conversely, *blinding*, in some circumstances, may not be feasible, for example in trials investigating the effect of some psychological treatments.

Let's try to exemplify the difference between *allocation concealment* and *blinding* and explain why both of them are so important. If someone is aware of the next treatment allocation, the selection of participating subjects might be - even unknowingly - influenced. For instance, if the referring clinician thinks that treatment A

is less effective than treatment B, and he/she knows that the next subjects will be allocated to treatment A and B, respectively, he/she may be inclined to chose a patient with mild symptoms for treatment A, and a patient with more severe symptoms for treatment B. Such inadequate *allocation concealment* may produce two groups of subjects that are not similar in terms of known and unknown prognostic factors (in this example they are not similar in terms of severity of illness), a phenomenon called selection bias (Schulz & Grimes, 2002). By contrast, the aim of *blinding* is to prevent *ascertainment bias*, that is the bias that might be introduced if trial participants (doctors, patients, outcome assessors) change their attitude towards the patients under treatment because they know what they are taking (Altman & Schulz, 2001).

Blinding can occur at the level of the patients, investigators, clinical trial nurses, outcome assessors or even biostatisticians (point B in the Figure). In medical journals it is often reported the term "double-blind". This term does not have a standard definition and cannot always be relied upon to convey which groups in an RCT were truly blind (www.consort-statement.org). One of the most frequent mistakes is to assume that *double-blind* means that the study subjects and clinicians were unaware as to which group subjects were allocated (Devereaux *et al.*, 2001). *Double-blind* might either refer to study subjects and investigators, or study subjects and outcome assessors, or outcome assessors and investigators, or any combination of groups involved. Because of this ambiguity, descriptions of blinding in reports of RCTs ideally should be explicit, describing precisely who was masked (Barbui *et al.*, 2007). Similarly, reports of *allocation concealment* should include a description of the method used with enough technical details to let readers determine the likelihood of the success of this process.

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