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ABOUT THE HANDBOOK

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of selection bias is relevant to the trial as a whole, and thus to all outcomes being compared. In contrast, control of detection bias is often outcome-specific and may be accomplished successfully for some outcomes in a study but not others. Thus, blinding up to allocation and blinding after allocation are addressing different sources of bias, are inherently different in their practicability and may apply to different components of a study. To clearly distinguish these different forms and purposes of 'blinding', we will refer to the process of concealing assignments as allocation concealment and reserve blinding for measures taken to reduce bias after the intervention has been assigned.

Empirical research has shown that lack of adequate allocation concealment is associated with bias (Chalmers 1983, Schulz 1995, Moher 1998a). Indeed, concealment has been found to be more important in preventing bias than other components of allocation, such as the generation of the allocation sequence (e.g., computer, random number table, alternation). Thus, studies can be judged on the method of allocation concealment. Information should be presented that provides some assurance that allocations were not known until, at least, the point of allocation. The method for assigning participants to interventions should be robust against patient and clinician bias and its description should be clear. The following are some approaches that can be used to ensure adequate concealment schemes.

- centralised (e.g. allocation by a central office unaware of subject characteristics) or pharmacy-controlled randomisation
- pre-numbered or coded identical containers which are administered serially to participants
- on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered
- sequentially numbered, sealed, opaque envelopes

Other approaches may include approaches similar to ones listed above, along with reassurance that the person who generated the allocation scheme did not administer it. Some schemes may be innovative and not fit any of the approaches above, but still provide adequate concealment.

Approaches to allocation concealment that should be considered clearly inadequate include: alternation; the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation, such as an open list of random numbers. When studies do not report any concealment approach, adequacy should be considered unclear. Examples include merely stating that a list or table was used, only specifying that sealed envelopes were used and reporting an apparently adequate concealment scheme in combination with other information that leads the reviewer to be suspicious. When reviewers enter studies into RevMan they are required to indicate whether allocation concealment was adequate (A), unclear (B), inadequate (C), or that allocation concealment was not used (D) as a criterion to assess validity.

6.4 Performance bias

Performance bias refers to systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation. To protect against unintended differences in care and placebo effects, those providing and receiving care can be 'blinded' so that they do not know the group to which the recipients of care have been allocated. Some research suggests that such blinding is important in protecting against bias (Karlowski 1975, Colditz 1989, Schulz 1995). Studies have shown that contamination (provision of the intervention to the control

group) and cointervention (provision of unintended additional care to either comparison group) can affect study results (CCSG 1978, Sackett 1979b). Furthermore, there is evidence that participants who are aware of their assignment status report more symptoms, leading to biased results (Karlowski 1975). For these reasons, reviewers may want to consider the use of ' blinding' as a criterion for validity. This can be done with the following questions: Were the recipients of care unaware of their assigned intervention? Were those providing care unaware of the assigned intervention?

A third question addressing blinding and detection bias is often added: Were persons responsible for assessing outcomes unaware of the assigned intervention? This addresses detection bias, as noted below.

Reviewers working on topics where blinding is likely to be important may want to develop specific criteria for judging the appropriateness of the method that was used for blinding. In some areas it may be desirable to use the same criterion across reviews, in which case a Collaborative Review Group (CRG) might want to agree to a standard approach for assessing blinding (Chalmers 1989, Schulz 1995, Jadad 1996, Moher 1996b).

6.5 Attrition bias

Attrition bias refers to systematic differences between the comparison groups in the loss of participants from the study. It has been called exclusion bias. It is called attrition bias here to prevent confusion with pre-allocation exclusion and inclusion criteria for enrolling participants. Because of inadequacies in reporting how losses of participants (e.g. withdrawals, dropouts, protocol deviations) are handled, reviewers should be cautious about implicit accounts of follow-up. The approach to handling losses has great potential for biasing the results and reporting inadequacies cloud this problem. What is reported, or more frequently implied, in study reports on attrition after allocation has not been found to be consistently related to bias (Schulz 1995). Thus reviewers should be cautious about using reported follow-up as a validity criterion, particularly when it is implied rather than explicitly reported. This is a general recommendation, however, and may not apply to certain topic areas that have higher quality reporting or where it is possible to obtain missing information from investigators.

6.6 Detection bias

Detection bias refers to systematic differences between the comparison groups in outcome assessment. Trials that blind the people who will assess outcomes to the intervention allocation should logically be less likely to be biased than trials that do not. Blinding is likely to be particularly important in research with subjective outcome measures such as pain (Karlowski 1975, Colditz 1989, Schulz 1995). However, at least two empirical studies have failed to demonstrate a relationship between blinding of outcome assessment and study results. This may be due to inadequacies in the reporting of studies (Reitman 1988).

Bias due to the selective reporting of results is different from bias in outcome assessment. This source of bias may be important in areas where multiple outcome measures are used, such as evaluations of treatments for rheumatoid arthritis (Gotzsche 1989). Therefore, reviewers may want to consider specification of predefined primary outcomes and analyses by the investigators as indicators of validity. Alternatively, selective reporting of particular outcomes could be taken to

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