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RESEARCH METHODS & REPORTING

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials

Flaws in the design, conduct, analysis, and reporting of randomised trials can cause the effect of an intervention to be underestimated or overestimated. The Cochrane Collaboration's tool for assessing risk of bias aims to make the process clearer and more accurate

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Development of risk assessment tool

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Further details on the items included in risk assessment tool (see http://www.bmj.com/content/343/bmj.d5928/suppl/DC1)

Cochrane Handbook.

Evaluation phase

Cochrane Library

The risk of bias tool

Principles for assessing risk of bias

1. Do not use quality scales

Quality scales and resulting scores are not an appropriate way to appraise clinical trials. They tend to combine assessments of aspects of the quality of reporting with aspects of trial conduct, and to assign weights to different items in ways that are difficult to justify. Both theoretical considerations[10] and empirical evidence[11] suggest that associations of different scales with intervention effect estimates are inconsistent and unpredictable

2. Focus on internal validity

The internal validity of a study is the extent to which it is free from bias. It is important to separate assessment of internal validity from that of external validity (generalisability or applicability) and precision (the extent to which study results are free from random error). Applicability depends on the purpose for which the study is to be used and is less relevant without internal validity. Precision depends on the number of participants and events in a study. A small trial with low risk of bias may provide very imprecise results, with a wide confidence interval. Conversely, the results of a large trial may be precise (narrow confidence interval) but have a high risk of bias if internal validity is poor

3. Assess the risk of bias in trial results, not the quality of reporting or methodological problems that are not directly related to risk of bias

The quality of reporting, such as whether details were described or not, affects the ability of systematic review authors and users of medical research to assess the risk of bias but is not directly related to the risk of bias. Similarly, some aspects of trial conduct, such as obtaining ethical approval or calculating sample size, are not directly related to the risk of bias. Conversely, results of a trial that used the best possible methods may still be at risk of bias. For example, blinding may not be feasible in many non-drug trials, and it would not be reasonable to consider the trial as low quality because of the absence of blinding. Nonetheless, many types of outcome may be influenced by participants' knowledge of the intervention received, and so the trial results for such outcomes may be considered to be at risk of bias because of the absence of blinding, despite this being impossible to achieve

4. Assessments of risk of bias require judgment

Assessment of whether a particular aspect of trial conduct renders its results at risk of bias requires both knowledge of the trial methods and a judgment about whether those methods are likely to have led to a risk of bias. We decided that the basis for bias assessments should be made explicit, by recording the aspects of the trial methods on which the judgment was based and then the judgment itself

5. Choose domains to be assessed based on a combination of theoretical and empirical considerations

Empirical studies show that particular aspects of trial conduct are associated with bias.[2 12] However, these studies did not include all potential sources of bias. For example, available evidence does not distinguish between different aspects of blinding (of participants, health professionals, and outcome assessment) and is very limited with regard to how authors dealt with incomplete outcome data. There may also be topic specific and design specific issues that are relevant only to some trials and reviews. For example, in a review containing crossover trials it might be appropriate to assess whether results were at risk of bias because there was an insufficient "washout" period between the two treatment periods

6. Focus on risk of bias in the data as represented in the review rather than as originally reported

Some papers may report trial results that are considered as at high risk of bias, for which it may be possible to derive a result at low risk of bias. For example, a paper that inappropriately excluded certain patients from analyses might report the intervention groups and outcomes for these patients, so that the omitted participants can be reinstated

7. Report outcome specific evaluations of risk of bias

Some aspects of trial conduct (for example, whether the randomised allocation was concealed at the time the participant was recruited) apply to the trial as a whole. For other aspects, however, the risk of bias is inherently specific to different outcomes within the trial. For example, all cause mortality might be ascertained through linkages to death registries (low risk of bias), while recurrence of cancer might have been assessed by a doctor with knowledge of the allocated intervention (high risk of bias)

Presentation of assessments

Assessments of risk of bias and synthesis of results

Summary assessment of risk of bias

Discussion

Development meeting participants (May 2005): Doug Altman (co-lead), Gerd Antes, Chris Cates, Jon Deeks, Peter Gøtzsche, Julian Higgins (co-lead), Sally Hopewell, Peter Jüni (organising committee), Steff Lewis, Philippa Middleton, David Moher (organising committee), Andy Oxman, Ken Schulz (organising committee), Nandi Siegfried, Jonathan Sterne, Simon Thompson.

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Evaluation meeting participants (March 2010): Doug Altman (organising committee), Elaine Beller, Sally Bell-Syer, Chris Cates, Rachel Churchill, June Cody, Jonathan Cook, Christian Gluud, Julian Higgins (organising committee), Sally Hopewell, Hayley Jones, Peter Jűni, Monica Kjeldstrøm, Toby Lasserson, Allyson Lipp, Lara Maxwell, Joanne McKenzie, Craig Ramsey, Barney Reeves, Jelena Savović (co-lead), Jonathan Sterne (co-lead), David Tovey, Laura Weeks (organising committee).

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Summary points

Systematic reviews should carefully consider the potential limitations of the studies included

The Cochrane Collaboration has developed a new tool for assessing risk of bias in randomised trials

The tool separates a judgment about risk of bias from a description of the support for that judgment, for a series of items covering different domains of bias

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Tables

Table 1| Cochrane Collaboration's tool for assessing risk of bias (adapted from Higgins and Altman13)

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere

*Assessments should be made for each main outcome or class of outcomes.

Table 2| **Example of risk of bias table from a Cochrane review14**

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was one to one with a block of size 6. The list of randomization was obtained using the SAS procedure plan at the data statistical analysis centre"
Allocation concealment (selection bias)	Unclear risk	The randomisation list was created at the statistical data centre, but further description of allocation is not included
Blinding of participants and researchers (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Losses to follow-up were disclosed and the analyses were conducted using, firstly, a modified intention to treat analysis in which missing=failures and, secondly, on an observed basis. Although the authors describe an intention to treat analysis, the 139 participants initially randomised were not all included; five were excluded (four withdrew and one had lung cancer diagnosed). This is a reasonable attrition and not expected to affect results. Adequate sample size of 60 per group was achieved
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	No description of the uptake of the therapeutic drug monitoring recommendations by physicians, which could result in performance bias

Table 3| Approach to formulating summary assessments of risk of bias for each important outcome (across domains) within and across trials (adapted from Higgins and Altman13)

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
High risk of bias	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Figure

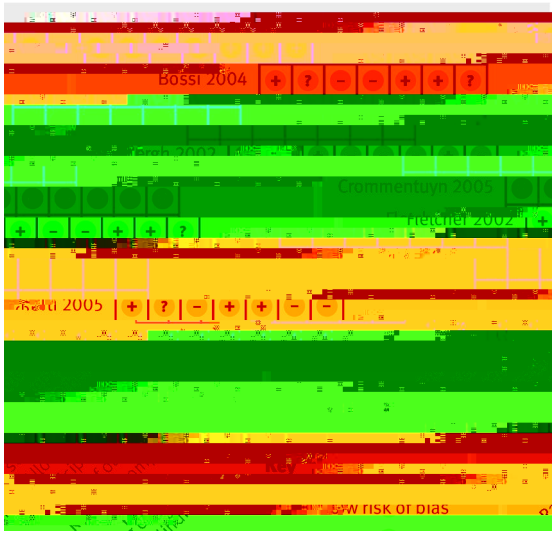

Fig 1 Example presentation of risk of bias assessments for studies in a Cochrane review of therapeutic monitoring of antiretroviral drugs in people with HIV[14]