

Chapter 8: Assessing risk of bias in included studies

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Key Points

- Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings; empirical evidence provides support for this concern.
- An assessment of the validity of studies included in a Cochrane Review should emphasize the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect.
- Numerous tools are available for assessing methodological quality of clinical trials. The use of scales that yield a summary score is emphatically discouraged.
- Cochrane recommends a specific tool for assessing risk of bias in each included study. This comprises a judgement and a support for the judgement for each entry in a ‘Risk

of bias' table, where each entry addresses a specific feature of the study. The judgement for each entry involves assessing the risk of bias as 'low risk', 'high risk, or 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias.

- Plots of 'Risk of bias' assessments can be created in Review Manager (RevMan).
- In clinical trials, biases can be categorized broadly as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases that do not fit into these categories.
- For parallel group trials, the features of interest in a standard 'Risk of bias' table of a Cochrane Review are sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias.
- Detailed considerations for the assessment of these features are provided in this chapter.

8.1 Introduction

The extent to which a Cochrane Review can draw conclusions about the effects of an intervention depends on whether the data and results from the included studies are valid. In particular, a meta-analysis of invalid studies may produce a misleading result, yielding a narrow confidence interval around the wrong intervention effect estimate. The evaluation of the validity of the included studies is therefore an essential component of a Cochrane Review, and should influence the analysis, interpretation and conclusions of the review.

The validity of a study may be considered to have two dimensions. The first dimension is whether the study is asking an appropriate research question. This is often described as 'external validity', and its assessment depends on the purpose for which the study is to be used. External validity is closely connected with the generalizability or applicability of a study's findings, and is addressed in Chapter 11 (Section 11.2.2) and Chapter 12 (Section 12.2).

The second dimension of a study's validity relates to whether it answers its research question 'correctly', that is, in a manner that is free from bias. This is often described as 'internal validity', and it is this aspect of validity that we address in this chapter. As most Cochrane Reviews focus on randomized trials, we concentrate on how to appraise the validity of this type of study. Chapter 13 addresses further issues in the assessment of non-randomized studies, and Chapter 14 includes further considerations for adverse effects. Assessments of internal validity are frequently referred to as 'assessments of methodological quality' or 'quality assessment'. However, we will avoid the term quality, for reasons that will be explained in Section 8.2.2. In the next section we define 'bias' and distinguish it from the related concepts of random error and quality.

8.2 What is bias?

8.2.1 'Bias' and 'risk of bias'

A **bias** is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect. Biases can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be entirely due to bias). Even a particular source of bias may vary in direction: bias due to a particular design flaw (e.g. lack of allocation concealment) may lead to underestimation of an effect in one study but overestimation in another study. It is usually impossible to know to what extent biases have affected the results of a particular study, although there is good empirical evidence that particular flaws in the design, conduct and analysis of randomized clinical trials lead to bias (see Section 8.2.3). In fact, as the results of a study may be unbiased despite a methodological flaw, it is more appropriate to consider **risk of bias**.

Differences in risks of bias can help explain variation in the results of the studies included in a systematic review (i.e. can explain heterogeneity of results). More rigorous studies are more likely to yield results that are closer to the truth. Meta-analysis of results from studies of variable validity can result in false positive conclusions (erroneously concluding an intervention is effective) if the less rigorous studies are biased toward overestimating an intervention's effect. They might also come to false negative conclusions (erroneously concluding no effect) if the less rigorous studies are biased towards underestimating an intervention's effect (Detsky 1992).

Cochrane Reviews must assess the risk of bias in all studies included in the review. This must be done irrespective of the anticipated variability in either the results or the validity of the included studies. For instance, the results may be consistent among studies but all the studies may be flawed. In this case, the review's conclusions should not be as strong as if a series of rigorous studies yielded consistent results about an intervention's effect. In a Cochrane Review, this appraisal process is described as the *assessment of risk of bias in included studies*. A tool that has been developed and implemented in RevMan for this purpose is described in Section 8.5. The rest of this chapter provides the rationale for this tool as well as explaining how bias assessments should be summarized and incorporated in analyses (Sections 8.6 to 8.8). Sections 8.9 to 8.15 provide background considerations to assist review authors in using the tool.

Bias should not be confused with **imprecision**. Bias refers to *systematic error*, meaning that multiple replications of the same study would reach the wrong answer on average. Imprecision refers to *random error*, meaning that multiple replications of the same study will produce different effect estimates because of sampling variation even if they would give the right answer on average. The results of smaller studies are subject to greater sampling variation and hence are less precise. Imprecision is reflected in the confidence interval around the intervention effect estimate from each study and in the weight given to the results of each study in a meta-analysis. More precise results are given more weight.

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8.2.2 'Risk of bias' and 'quality'

Bias may be distinguished from **quality**. The phrase 'assessment of methodological quality' has been used extensively in the context of systematic review methods to refer to the critical appraisal of included studies. The term suggests an investigation of the extent to which study authors conducted their research to the highest possible standards. This *Handbook* draws a distinction between assessment of methodological quality and assessment of risk of bias, and recommends a focus on the latter. The reasons for this distinction include:

- The key consideration in a Cochrane Review is the extent to which results of included studies should be *believed*. Assessing risk of bias targets this question squarely.
- A study may be performed to the highest possible standards yet still have an important risk of bias. For example, in many situations it is impractical or impossible to blind participants or study personnel regarding intervention group. It is inappropriately judgemental to describe all such studies as of 'low quality', but that does not mean they are free of bias resulting from knowledge of intervention status.
- Some markers of quality in medical research, such as obtaining ethical approval, performing a sample size calculation and reporting a study in line with the CONSORT Statement (Schulz 2010), are unlikely to have direct implications for risk of bias.
- An emphasis on risk of bias overcomes ambiguity between the quality of reporting and the quality of the underlying research (although does not overcome the problem of having to rely on reports to assess the underlying research).

Notwithstanding these concerns about the term 'quality', the term 'quality of evidence' is used in 'Summary of findings' tables in Cochrane Reviews to describe the extent to which one can be confident that an estimate of effect is near the true value for an outcome, across studies, as described in Chapter 11 (Section 11.5) and Chapter 12 (Section 12.2). The risk of bias in the results of each study contributing to an estimate of effect is one of several factors that must be considered when judging the quality of a body of evidence, as defined in this context.

8.2.3 Establishing empirical evidence of biases

Biases associated with particular characteristics of studies may be examined using a technique often known as **meta-epidemiology** (Naylor 1997, Sterne 2002). A meta-epidemiological study analyses a collection of meta-analyses, in each of which the component studies have been classified according to some study-level characteristic. An early example was the study of clinical trials with dichotomous outcomes included in meta-analyses from the *Cochrane Pregnancy and Childbirth Database* (Schulz 1995a). This study demonstrated that trials in which randomization was inadequately concealed or inadequately reported yielded exaggerated estimates of intervention effect compared with trials that reported adequate concealment, and found a similar (but smaller) association for trials that were not described as 'double-blind'.

A simple analysis of a meta-epidemiological study is to calculate the ‘ratio of odds ratios’ within each meta-analysis (for example, the intervention odds ratio in trials with inadequate/unclear allocation concealment divided by the odds ratio in trials with adequate allocation concealment). These ratios of odds ratios are then combined across meta-analyses, in a meta-analysis. Thus, such analyses are also known as ‘meta-meta-analyses’. In subsequent sections of this chapter, empirical evidence of bias from meta-epidemiological studies is cited where available as part of the rationale for assessing each domain of potential bias.

8.3 Tools for assessing quality and risk of bias

8.3.1 Types of tools

Many tools have been proposed for assessing the quality of studies for use in the context of a systematic review and elsewhere. Most tools are **scales**, in which various components of quality are scored and combined to give a summary score; or **checklists**, in which specific questions are asked (Jüni 2001).

In 1995, Moher and colleagues identified 25 scales and nine checklists that had been used to assess the validity or ‘quality’ of randomized trials (Moher 1995, Moher 1996). These scales and checklists included between three and 57 items and were found to take from 10 to 45 minutes to complete for each study. Almost all of the items in the instruments were based on suggested or generally accepted criteria that were mentioned in textbooks. Many instruments also contained items that were not directly related to internal validity, such as whether a power calculation was done (an item that relates more to the precision of the results) or whether the inclusion and exclusion criteria were clearly described (an item that relates more to applicability than validity). Scales were more likely than checklists to include criteria that did not relate directly to internal validity.

The Cochrane recommended tool for assessing risk of bias is neither a scale nor a checklist. It is a **domain-based evaluation** in which critical assessments are made separately for different domains, and is described in Section 8.5. It was developed between 2005 and 2007 by a working group of methodologists, editors and review authors. Since it is impossible to know the extent of bias (or even the true risk of bias) in a given study, the possibility of validating any proposed tool is limited. The most realistic assessment of the validity of a study may involve subjectivity: for example an assessment of whether lack of blinding of patients might plausibly have affected recurrence of a serious condition such as cancer.

8.3.2 Reporting versus conduct

A key difficulty in the assessment of risk of bias or quality is the obstacle provided by incomplete reporting. While the emphasis should be on the risk of bias in the actual design and conduct of a study, it can be tempting to resort to assessing the adequacy of reporting. Many of the tools reviewed in Moher 1995 were liable to confuse these separate issues. Moreover, scoring in scales was often based on whether something was reported (such as stating how participants were allocated) rather than whether it was done appropriately in the study.

8.3.3 Quality scales and Cochrane Reviews

The use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane Reviews. While the approach offers appealing simplicity, it is not supported by empirical evidence (Emerson 1990, Schulz 1995a). Calculating a summary score inevitably involves assigning ‘weights’ to different items in the scale, and it is difficult to justify the weights assigned. Furthermore, scales have been shown to be unreliable assessments of validity (Jüni 1999), and they are less likely to be transparent to users of the review. It is preferable to use simple approaches for assessing validity that can be fully reported (i.e. how each trial was rated on each criterion).

One commonly-used scale was developed by Jadad and colleagues for randomized trials in pain research (Jadad 1996). The use of this scale is explicitly discouraged. As well as suffering from the generic problems of scales, it has a strong emphasis on reporting rather than conduct, and does not cover one of the most important potential biases in randomized trials, namely allocation concealment (see Section 8.10).

8.3.4 Collecting information for assessments of risk of bias

Despite the limitations of reports, information about the design and conduct of studies will often be obtained from published reports, including journal papers, book chapters, dissertations, conference abstracts and websites (including trials registries). Published protocols are a particularly valuable source of information when they are available. The extraction of information from such reports is discussed in Chapter 7. Data collection forms should include space to extract sufficient details to allow implementation of the Cochrane ‘Risk of bias’ tool (Section 8.5). When extracting this information, it is highly desirable to record the source of each piece of information (including the precise location within a document). It is helpful to test data collection forms and assessments of risk of bias within a review team on a pilot sample of articles to ensure that criteria are applied consistently, and that consensus can be reached. Three to six papers that, if possible, span a range from low to high risk of bias might provide a suitable sample for this.

Authors must also decide whether those assessing risk of bias will be blinded to the names of the authors, institutions, journal and results of a study when they assess its methods. One study suggested that blind assessment of reports might produce lower and more consistent ratings than open assessments (Jadad 1996), whereas other studies suggested little benefit from blind assessments (Berlin 1997, Kjaergard 2001). Blinded assessments are very time consuming, they may not be possible when the studies are well known to the review authors, and not all domains of bias can be assessed independently of the outcome data. Furthermore, knowledge of who undertook a study can sometimes allow reasonable assumptions to be made about how the study was conducted (although such assumptions must be reported by the review author). Authors must weigh the potential benefits against the costs involved when deciding whether or not to blind assessment of certain information in study reports.

Review authors with different levels of methodological training and experience may identify different sources of evidence and reach different judgements about risk of bias. Although experts in content areas may have preformed opinions that can influence their assessments (Oxman 1993), nonetheless, they may give more consistent assessments of

the validity of studies than people without content expertise (Jadad 1996). Content experts may have valuable insights into the magnitudes of biases, and experienced methodologists may have valuable insights into potential biases that are not at first apparent. ‘Risk of bias’ assessments in Cochrane Reviews must be made independently by at least two people, with the process for resolving disagreements defined in advance. It is desirable that review authors should include both content experts and methodologists and ensure that all have an adequate understanding of the relevant methodological issues.

Attempts to assess risk of bias are often hampered by incomplete reporting of what happened during the conduct of the study. One option for collecting missing information is to contact the study investigators. Unfortunately, contacting authors of trial reports may lead to overly positive answers. In a survey of 104 trialists, using direct questions about blinding with named categories of trial personnel, 43% responded that the data analysts in their double-blind trials were blinded, and 19% responded that the manuscript writers were blinded (Haahr 2006). This is unlikely to be true, given that such procedures were reported in only 3% and 0% of the corresponding published articles, and that they are very rarely described in other trial reports.

To reduce the risk of overly positive answers, review authors should use open-ended questions when asking trial authors for information about study design and conduct. For example, to obtain information about blinding, a request of the following form might be appropriate: “Please describe all measures used, if any, to ensure blinding of trial participants and key trial personnel from knowledge of which intervention a participant had received.” To obtain information about the randomization process, a request of the following form might be appropriate: “How did you decide which intervention the next patient should get?” More focused questions can then be asked to clarify remaining uncertainties.

8.4 Introduction to sources of bias in clinical trials

The reliability of the results of a randomized trial depends on the extent to which potential sources of bias have been avoided. A key part of a review is to consider the risk of bias in the results of each of the eligible studies. A useful classification of biases is into selection bias, performance bias, attrition bias, detection bias and reporting bias. In this section we describe each of these biases and introduce seven corresponding domains that are assessed in the Cochrane ‘Risk of bias’ tool. These are summarized in Table 8.4.a. We describe the tool for assessing the seven domains in Section 8.5. We provide more detailed consideration of each issue in Sections 8.9 to 8.15.

8.4.1 Selection bias

Selection bias refers to systematic differences between baseline characteristics of the groups that are compared. The unique strength of randomization is that, if successfully accomplished, it prevents selection bias in allocation of interventions to participants. Its success in this respect depends on fulfilling several interrelated processes. A rule for allocating interventions to participants must be specified, based on some chance

(random) process. We call this **sequence generation**. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process is often termed **allocation concealment**, although could more accurately be described as allocation sequence concealment. Thus, one suitable method for assigning interventions would be to use a simple random (and therefore unpredictable) sequence, and to conceal the upcoming allocations from those involved in enrolment into the trial.

8.4.2 Performance bias

Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest. After enrolment into the study, **blinding (or masking) of study participants and personnel** may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes. Effective blinding can also ensure that the groups being compared receive a similar amount of attention, ancillary treatment and diagnostic investigations. Blinding is not always possible, however. For example, it is usually impossible to blind people to whether or not major surgery has been undertaken.

8.4.3 Detection bias

Detection bias refers to systematic differences between groups in how outcomes are determined. **Blinding (or masking) of outcome assessors** may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes, such as degree of postoperative pain.

8.4.4 Attrition bias

Attrition bias refers to systematic differences between groups in withdrawals from a study. Withdrawals from the study lead to **incomplete outcome data**. There are two reasons for withdrawals or incomplete outcome data in clinical trials. *Exclusions* refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to the trialists. *Attrition* refers to situations in which outcome data are not available.

8.4.5 Reporting bias

Reporting bias refers to systematic differences between reported and unreported findings. Within a published report those analyses with statistically significant differences between intervention groups are more likely to be reported than non-significant differences. This sort of 'within-study publication bias' is usually known as outcome reporting bias or **selective reporting bias**, and may be one of the most substantial biases affecting results from individual studies (Chan 2005).

8.4.6 Other biases

In addition there are **other sources of bias** that are relevant only in certain circumstances. These relate mainly to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster-randomized trials); some can be found across a broad spectrum of trials, but only for specific circumstances (e.g. contamination, whereby the

experimental and control interventions get ‘mixed’, for example if participants pool their drugs); and there may be sources of bias that are only found in a particular clinical setting.

For all potential sources of bias, it is important to consider the likely magnitude and direction of the bias. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases.

Table 8.4.a: A common classification scheme for bias

Type of bias	Description	Relevant domains in the Cochrane ‘Risk of bias’ tool
Selection bias	Systematic differences between baseline characteristics of the groups that are compared	<ul style="list-style-type: none"> • Sequence generation • Allocation concealment
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest	<ul style="list-style-type: none"> • Blinding of participants and personnel • Other potential threats to validity
Detection bias	Systematic differences between groups in how outcomes are determined	<ul style="list-style-type: none"> • Blinding of outcome assessment • Other potential threats to validity
Attrition bias	Systematic differences between groups in withdrawals from a study	<ul style="list-style-type: none"> • Incomplete outcome data
Reporting bias	Systematic differences between reported and unreported findings	<ul style="list-style-type: none"> • Selective outcome reporting (see also Chapter 10)

8.5 The Cochrane tool for assessing risk of bias

8.5.1 Overview

This section describes the approach that must be used for assessing risk of bias in randomized studies included in Cochrane Reviews. It is a two-part tool, addressing the seven specific domains discussed in Sections 8.9 to 8.15 (namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and (optionally) ‘other issues’). The tool is summarized in Table 8.5.a. Note that the tool was revised in late 2010 after an evaluation project. Changes made at that point are summarized in Table 8.5.b.

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Each domain in the tool includes one or more specific entries in a ‘Risk of bias’ table. Within each entry, the first part of the tool describes what was reported to have happened in the study, in sufficient detail to support a judgement about the risk of bias. The second part of the tool assigns a judgement relating to the risk of bias for that entry. This is achieved by assigning a judgement of ‘low risk’ of bias, ‘high risk’ of bias, or ‘unclear risk’ of bias.

The domains of sequence generation, allocation concealment and selective outcome reporting should each be addressed in the tool by a single entry for each study. For blinding of participants and personnel, blinding of outcome assessment and for incomplete outcome data, two or more entries may be used because assessments generally need to be made separately for different outcomes (or for the same outcome at different time points). Review authors should try to limit the number of entries used by grouping outcomes, for example, as ‘subjective’ or ‘objective’ outcomes for the purposes of assessing blinding of outcome assessment; or as ‘patient-reported at six months’ or ‘patient-reported at 12 months’ for incomplete outcome data. The same groupings of outcomes will be applied to every study in the review. The final domain (‘other bias’) can be assessed as a single entry for studies as a whole (this is the default setting in RevMan). However, it is strongly recommended that prespecified entries be used to address specific other risks of bias. Such author-specified entries may be for studies as a whole or for individual (or grouped) outcomes within every study.

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Table 8.5.a: The Cochrane tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
<i>Selection bias</i>		
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.	Risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Risk of selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
<i>Performance bias</i>		
Blinding of participants and personnel <i>Assessments should be made for each main outcome (or class of outcomes).</i>	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
<i>Detection bias</i>		
Blinding of outcome assessment <i>Assessments should be made for each main</i>	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Risk of detection bias due to knowledge of the allocated interventions by outcome assessors.

<i>outcome (or class of outcomes).</i>		
<i>Attrition bias</i>		
Incomplete outcome data <i>Assessments should be made for each main outcome (or class of outcomes).</i>	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 randomized participants), reasons for attrition/exclusions (where reported), and any reinclusions in analyses performed by the review authors.	Risk of attrition bias due to amount, nature or handling of incomplete outcome data.
<i>Reporting bias</i>		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Risk of reporting bias due to selective outcome reporting.
<i>Other bias</i>		
Other sources of bias	State any important concerns about bias that are not addressed in the other domains of the tool. If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry.	Risk of bias due to problems not covered elsewhere in the table.

Table 8.5.b: Differences between the ‘Risk of bias’ tool described in *Handbook* versions 5.0.1/5.0.2 and the revised ‘Risk of bias’ tool described in *Handbook* version 5.1/5.2 (this version)

Separation of blinding	In the earlier version of the tool, biases related to blinding of participants, personnel and outcome assessors were all assessed within a single domain (although they may have been assessed separately for different outcomes). In the revised tool, bias related to blinding of participants and personnel is assessed in a separate domain from bias related to blinding of outcome assessment.
Nature of the judgement	The judgements are now expressed simply as ‘low risk’, ‘high risk’ or ‘unclear risk’ of bias. The domains are no longer expressed as questions, and the responses ‘Yes’ indicating low risk of bias and ‘No’ indicating high risk of bias have been removed.
Minor rewording	<p>The items have been renamed in RevMan with the removal of question-based judgements:</p> <p><i>‘Adequate sequence generation?’</i> became <i>‘Random sequence generation’</i>.</p> <p><i>‘Allocation concealment?’</i> became <i>‘Allocation concealment’</i>.</p> <p><i>‘Blinding?’</i> became <i>‘Blinding of participants and personnel’</i> and <i>‘Blinding of outcome assessment’</i>.</p> <p><i>‘Incomplete outcome data addressed?’</i> became <i>‘Incomplete outcome data’</i>.</p> <p><i>‘Free of selective reporting?’</i> became <i>‘Selective reporting’</i>.</p> <p><i>‘Free of other bias?’</i> became <i>‘Other bias’</i>.</p>
Insertion of categories of bias	The revised tool clarifies the category of bias within which each domain falls: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias.
Reconsideration of eligible issues for other	The guidance for the other bias domain has been edited to strengthen the guidance that additional items should be used only exceptionally, and that these items should relate

bias, including early stopping of a trial	to issues that may lead directly to bias. In particular, the mention of early stopping of a trial has been removed, because: 1) simulation evidence suggests that inclusion of trials that stopped early in meta-analyses will not lead to substantial bias, and 2) exclusion of trials that stopped early has the potential to bias meta-analyses towards the null (as well as leading to loss of precision).
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8.5.2 The support for judgement

All judgements of risk of bias in the ‘Risk of bias’ tool must be supported by a succinct summary of the evidence or rationale underlying the judgement. This aims to ensure transparency in how these judgements are reached. The source of information in the supporting statement should be made clear. For a specific study, information for the support for a judgement will often come from a single published study report, but may be obtained from a mixture of study reports, protocols, published comments on the study and contacts with the investigators. Where appropriate, the support for judgement should include verbatim quotes from reports or correspondence. Alternatively, or in addition, it may include a summary of known facts, or a comment from the review authors. In particular, it should include other information that influences any judgements made (such as knowledge of other studies performed by the same investigators). A helpful construction to supplement an ambiguous quote is to state ‘Probably done’ or ‘Probably not done’, providing the rationale for such assertions. When no information is available from which to make a judgement, this should be stated explicitly. Examples of proposed formatting for the description are provided in Table 8.5.c.

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Table 8.5.c: Examples of supports for judgement for sequence generation entry (fictional)

Sequence generation	Comment: No information provided.
Sequence generation	Quote: “patients were randomly allocated”.
Sequence generation	Quote: “patients were randomly allocated”. Comment: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).
Sequence generation	Quote: “patients were randomly allocated”. Comment: Probably not done, as a similar trial by these investigators included the same phrase yet used alternate allocation (Winrow 1983).
Sequence generation	Quote (from report): “patients were randomly allocated”.

Quote (from correspondence): “Randomization was performed according to day of treatment”.

Comment: not randomized

8.5.3 The judgement

Review authors’ judgements should be categorized as ‘low risk’ of bias, ‘high risk’ of bias or ‘unclear risk’ of bias. The assessments should consider the risk of *material* bias rather than *any* bias. We define ‘material bias’ as bias of sufficient magnitude to have a notable impact on the results or conclusions of the trial, recognizing that subjectivity is involved in any such judgement.

Table 8.5.d provides criteria for making judgements about risk of bias from each of the seven domains in the tool. If insufficient detail about what happened in the study is reported, the judgement will usually be ‘unclear risk’ of bias. An ‘unclear’ judgement should also be made if what happened in the study is known, but the risk of bias is unknown; or if an entry is not relevant to the study at hand (particularly for assessing blinding and incomplete outcome data, when the outcome being assessed by the entry has not been measured in the study).

Table 8.5.d: Criteria for judging risk of bias in the ‘Risk of bias’ assessment tool

Random sequence generation

Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence

<p>Criteria for a judgement of ‘low risk’ of bias</p>	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> • referring to a random number table; • using a computer random number generator; • coin tossing; • shuffling cards or envelopes; • throwing dice; • drawing of lots; • minimization.* <p>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.</p>
<p>Criteria for the judgement of ‘high risk’ of bias</p>	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> • sequence generated by odd or even date of birth;

	<ul style="list-style-type: none"> • sequence generated by some rule based on date (or day) of admission; • sequence generated by some rule based on hospital or clinic record number. <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned here and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:</p> <ul style="list-style-type: none"> • allocation by judgement of the clinician; • allocation by preference of the participant; • allocation based on the results of a laboratory test or a series of tests; • allocation by availability of the intervention.
Criteria for the judgement of 'unclear risk' of bias	Insufficient information about the sequence generation process available to permit a judgement of 'low risk' or 'high risk'.

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment

Criteria for a judgement of 'low risk' of bias	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:</p> <ul style="list-style-type: none"> • central allocation (including telephone, web-based and pharmacy-controlled randomization); • sequentially numbered drug containers of identical appearance;
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	<ul style="list-style-type: none"> • sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'high risk' of bias	<p>Participants or investigators enrolling participants could possibly foresee assignments, and thus introduce selection bias, due to allocation based on:</p> <ul style="list-style-type: none"> • use of an open random allocation schedule (e.g. a list of random numbers); • use of assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • alternation or rotation; • date of birth; • case record number; • any other explicitly unconcealed procedure.
Criteria for the judgement of 'unclear risk' of bias	<p>Insufficient information available to permit a judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes was described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.</p>

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Criteria for a judgement of 'low risk' of bias	Either of the following:
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	<ul style="list-style-type: none"> • no blinding or incomplete blinding, but the review authors judge that the outcome was not likely to be influenced by lack of blinding; • blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'high risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; • blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.
Criteria for the judgement of 'unclear risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • insufficient information available to permit a judgement of 'low risk' or 'high risk'; • the study did not address this outcome.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors

Criteria for a judgement of 'low risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • no blinding of outcome assessment, but the review authors judge that the outcome measurement was not likely to be influenced by lack of blinding; • blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
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Criteria for the judgement of 'high risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; • blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.
Criteria for the judgement of 'unclear risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • insufficient information available to permit a judgement of 'low risk' or 'high risk'; • the study did not address this outcome.

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data

Criteria for a judgement of 'low risk' of bias	<p>Any one of the following:</p> <ul style="list-style-type: none"> • no missing outcome data; • reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
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	<ul style="list-style-type: none"> • for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have had a clinically relevant impact on the intervention effect estimate; • for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not enough to have had a clinically relevant impact on the observed effect size; • missing data have been imputed using appropriate methods.
Criteria for the judgement of 'high risk' of bias	<p>Any one of the following:</p> <ul style="list-style-type: none"> • reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to have induced clinically relevant bias in the intervention effect estimate; • for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is enough to have induced clinically relevant bias in the observed effect size; • 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • potentially inappropriate application of simple imputation.
Criteria for the judgement of 'unclear risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • insufficient reporting of attrition/exclusions to permit a judgement of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided);

- the study did not address this outcome.

Selective reporting

Reporting bias due to selective outcome reporting

Criteria for a judgement of 'low risk' of bias	<p>Either of the following:</p> <ul style="list-style-type: none"> • the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; • the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'high risk' of bias	<p>Any one of the following:</p> <ul style="list-style-type: none"> • not all of the study's prespecified primary outcomes have been reported; • one or more primary outcomes have been reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; • one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • one or more outcomes of interest in the review have been reported incompletely so that they cannot be entered in a meta-analysis;

	<ul style="list-style-type: none"> the study report failed to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'unclear risk' of bias	Insufficient information available to permit a judgement of 'low risk' or 'high risk'. It is likely that the majority of studies will fall into this category.

Other bias

Bias due to problems not covered elsewhere in the table

Criteria for a judgement of 'low risk' of bias	The study appears to be free of other sources of bias.
Criteria for the judgement of 'high risk' of bias	<p>There is at least one important risk of bias. For example, the study:</p> <ul style="list-style-type: none"> had a potential source of bias related to the specific study design used; has been claimed to have been fraudulent; had some other problem.
Criteria for the judgement of 'unclear' risk of bias	<p>There may be a risk of bias, but there is either:</p> <ul style="list-style-type: none"> insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

8.6 Presentation of assessments of risk of bias

A ‘Risk of bias’ table is available in RevMan for inclusion in a Cochrane Review as part of the ‘Characteristics of included studies’ table. For each entry, the judgement (‘low risk’ of bias; ‘high risk’ of bias, or ‘unclear risk’ of bias) is followed by a text box for a description of the design, conduct or observations that underlie the judgement. Figure 8.6.a provides an example of how it might look. If the text box is left empty, and the judgement is left as ‘unclear risk’, then the entry will be omitted from the ‘Risk of bias’ table for the study on publication in the *Cochrane Database of Systematic Reviews (CDSR)*.

Considerations for presentation of ‘Risk of bias’ assessments in the review text are discussed in Chapter 4 (Section 4.5; under the Results subheading ‘Risk of bias in included studies’ and the Discussion subheading ‘Quality of the evidence’).

Three types of figures may be generated using RevMan to present ‘Risk of bias’ assessments in a published review. Firstly, a ‘Risk of bias’ graph illustrates the proportion of studies with each of the judgements (‘low risk’, ‘high risk’, ‘unclear risk’ of bias) for each entry in the tool (see Figure 8.6.b). Secondly, a ‘Risk of bias’ summary figure presents all of the judgements in a cross-tabulation of study by entry (see Figure 8.6.c). Thirdly (in RevMan 5.3 onwards), a standard forest plot can present the judgements as they appear in the ‘Risk of bias’ summary figure, alongside the results for each study. Where different judgements have been recorded for different outcome groups (i.e. for performance bias, detection bias, attrition bias and any user-defined domains assigned to assessment at the outcome level, as indicated in Section 8.5.1), the outcome illustrated in the forest plot must be linked to the correct outcome-level ‘Risk of bias’ assessments within RevMan.

An alternative, and perhaps preferable, version of the first figure (the ‘Risk of bias’ graph) would be to restrict attention to studies in a particularly important meta-analysis, and to represent the proportion of information (rather than the proportion of studies) at low risk, unclear risk and high risk of bias. The proportion of information may be measured by the sums of weights awarded to the studies in the meta-analysis. Currently, however, such plots cannot be produced within RevMan.

Figure 8.6.a: Example of a ‘Risk of bias’ table for a single study (fictional)

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “patients were randomly allocated.” Comment: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).
Allocation concealment (selection bias)	High risk	Quote: “. . . using a table of random numbers.” Comment: probably not done

Blinding of participants and personnel (performance bias)	Low risk	Quote: “double blind, double dummy”; “High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available (the success of blinding was evaluated by examining the drugs before distribution).” Comment: probably done
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low risk	Quote: “double blind” Comment: probably done
Blinding of outcome assessment (detection bias; all-cause mortality)	Low risk	Obtained from medical records; review authors do not believe this will introduce bias.
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	High risk	4 weeks: 17/110 missing from intervention group (9 due to 'lack of efficacy'); 7/113 missing from control group (2 due to 'lack of efficacy').
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	High risk	12 weeks: 31/110 missing from intervention group; 18/113 missing from control group. Reasons differed across groups.
Selective reporting (reporting bias)	High risk	Three rating scales for cognition listed in Methods, but only one (with statistically significant results) was reported.

Figure 8.6.b: Example of a ‘Risk of bias’ graph

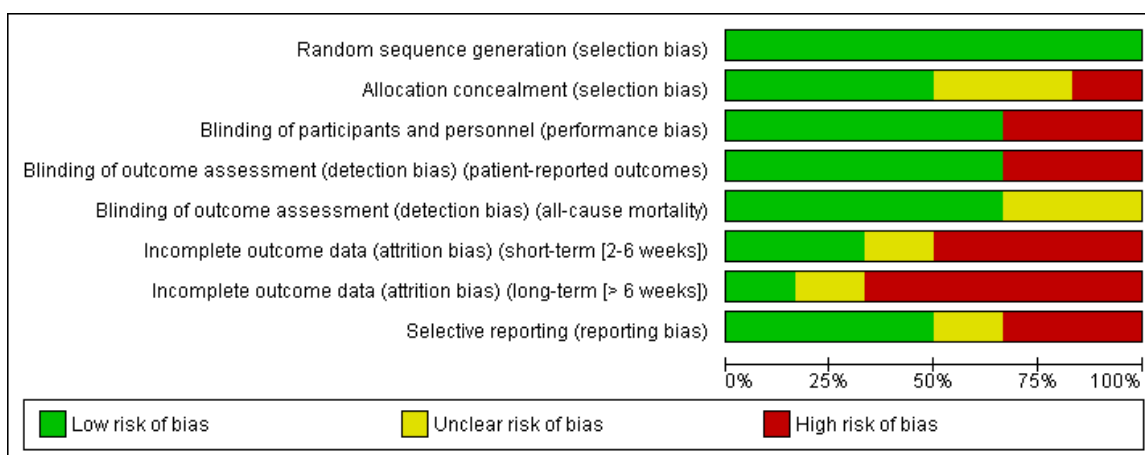


Figure 8.6.c: Example of a 'Risk of bias' summary figure

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (all-cause mortality)	Incomplete outcome data (attrition bias) (short-term [2-6 weeks])	Incomplete outcome data (attrition bias) (long-term [≥ 6 weeks])	Selective reporting (reporting bias)
Barry 1988	+	-	+	+	+	-	-	-
Baylis 1989	+	+	+	+	+	?	?	+
Cooper 1987	+	?	-	-	?	-	-	+
Dodd 1985	+	?	+	+	+	+	-	?
Goodwin 1986	+	+	+	+	+	+	+	+
Sanders 1983	+	+	-	-	?	-	-	-

8.7 Summary assessments of risk of bias

Cochrane’s recommended tool for assessing risk of bias in included studies involves the assessment and presentation of individual domains, such as allocation concealment and blinding. To draw conclusions about the overall risk of bias for an outcome it is necessary to summarize these. The use of scales (in which scores for multiple items are added up to produce a total) is discouraged for reasons outlined in Section 8.3.1.

Nonetheless, any assessment of the overall risk of bias involves consideration of the relative importance of different domains. A review author will have to make judgements

about which domains are most important in the current review. For example, for highly subjective outcomes such as pain, authors may decide that blinding of participants is critical. How such judgements are reached should be made explicit and they should be informed by:

- **Empirical evidence of bias:** Sections 8.5 to 8.15 summarize empirical evidence of the association between domains such as allocation concealment and blinding and estimated magnitudes of effect. However, the evidence base remains incomplete.
- **Likely direction of bias:** The available empirical evidence suggests that failure to meet most criteria, such as adequate allocation concealment, is associated with overestimates of effect. If the likely direction of bias for a domain is such that effects will be underestimated (biased towards the null), then, providing the review demonstrates an important effect of the intervention, such a domain may be of less concern.
- **Likely magnitude of bias:** The likely magnitude of bias associated with any domain may vary. For example, the magnitude of bias associated with inadequate blinding of participants is likely to be greater for more subjective outcomes. Some indication of the likely magnitude of bias may be provided by the empirical evidence base (see above), but this does not yet provide clear information about the particular scenarios in which biases may be large or small. It may, however, be possible to consider the likely magnitude of bias relative to the estimated magnitude of effect. For example, inadequate allocation sequence concealment and a small estimate of effect might substantially reduce confidence in the estimate, whereas minor inadequacies in how incomplete outcome data were addressed might not reduce confidence in a large estimate of effect substantially.

Summary assessment of risk of bias might be considered at four levels:

- **Summarizing risk of bias for a study across outcomes:** Some domains affect the risk of bias across outcomes in a study: e.g. sequence generation and allocation sequence concealment. Other domains, such as blinding and incomplete outcome data, may have different risks of bias for different outcomes within a study. Thus, review authors should not assume that the risk of bias is the same for all outcomes in a study. Moreover, a summary assessment of the risk of bias across all outcomes for a study is generally of little interest.
- **Summarizing risk of bias for an outcome within a study (across domains):** This is the recommended level at which to summarize the risk of bias in a study, because some risks of bias may be different for different outcomes. Indeed, it is highly recommended that risk of bias is summarized at this level. A summary assessment of the risk of bias for an outcome should include all of the entries relevant to that outcome: i.e. both study-level entries, such as allocation sequence concealment, and outcome specific entries, such as blinding.
- **Summarizing risk of bias for an outcome across studies (e.g. for a meta-analysis):** These are the main summary assessments that will be made by review authors and

incorporated into judgements about the quality of evidence in ‘Summary of findings’ tables, as described in Chapter 11 (Section 11.2). As explained in Section 8.8, including study results at high risk of bias in a meta-analysis may lead to the quality of evidence being lower than if such trials were excluded.

- Summarizing risk of bias for a review as a whole (across studies and outcomes):**
 Summarizing the overall risk of bias in a review should be avoided for two reasons. Firstly, this requires value judgements about which outcomes are critical to a decision. Frequently no data are available from the studies included in a review for some outcomes that may be critical, such as adverse effects, and the risk of bias is rarely the same across all outcomes that are critical to such an assessment. Secondly, judgements about which outcomes are critical to a decision may vary from setting to setting, because of differences in both societal values and other factors, such as baseline risk. Judgements about the overall risk of bias of evidence across studies and outcomes should be made in a specific context, for example in the context of clinical practice guidelines, and not in the context of systematic reviews that are intended to inform decisions across a variety of settings.

Review authors should make explicit judgements about the risk of bias for important outcomes both within and across studies. This requires identifying the most important domains (‘key domains’) that feed into these summary assessments. Table 8.7.a provides a possible approach to making summary assessments of the risk of bias for important outcomes within and across studies.

Table 8.7.a: Possible approach for *summary assessments* of the risk of bias for each important outcome (across domains) within and across studies

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias.
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias.
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the

8.8 Incorporating assessments into analyses

8.8.1 Introduction

Statistical considerations often involve a trade-off between bias and precision. A meta-analysis that includes all eligible studies may produce a result with high precision (narrow confidence interval), but be seriously biased because of flaws in the conduct of some of the studies. On the other hand, including only the studies at low risk of bias in all domains assessed may produce a result that is unbiased but imprecise (if there are only a few high-quality studies).

When performing and presenting meta-analyses, review authors must address risk of bias in the results of included studies, and when randomized studies are involved, this must be based on the Cochrane ‘Risk of bias’ tool. It is not appropriate to present analyses and interpretations based on all studies, ignoring flaws identified during the assessment of risk of bias. The higher the proportion of studies assessed to be at high risk of bias, the more cautious should be the analysis and interpretation of their results, and the lower will be the grading of the quality of the evidence.



8.8.2 Exploring the impact of risk of bias

8.8.2.1 Graphing results according to risk of bias

The discussion that follows applies both individual bias domains and to risk of bias summarized at the study level (see Section 8.7). Plots of intervention effect estimates (e.g. forest plots) stratified according to risk of bias are likely to be a useful way to begin examining the potential for bias to affect the results of a meta-analysis. Forest plots ordered by judgements on each ‘Risk of bias’ entry are available in RevMan 5. Such plots give a visual impression of the relative contributions of the studies at low, unclear and high risk of bias, and also of the extent of differences in intervention effect estimates between studies at low, unclear and high risk of bias. It is usually sensible to restrict such plots to key bias domains (see Section 8.7).

8.8.2.2 Studies assessed as at unclear risk of bias

Studies are assessed as being at an unclear risk of bias when too few details are available to make a judgement of ‘high’ or ‘low’ risk; when the risk of bias is genuinely unknown despite sufficient information about the conduct; or when an entry is not relevant to a study (for example because the study did not address any of the outcomes in the group of outcomes to which the entry applies). When the first reason dominates, it is reasonable to assume that the average bias in results from such studies will be less than in studies at a high risk of bias, because the conduct of some studies assessed as unclear will in fact have avoided bias. Limited evidence from empirical studies that examined the ‘high’ and ‘unclear’ categories separately confirms this: for example, the Schulz 1995a study found that intervention odds ratios were exaggerated by 41% for trials with inadequate

concealment (high risk of bias) and by 30% for trials with unclear concealment (unclear risk of bias). However, most empirical studies combined the ‘high’ and ‘unclear’ categories, which were then compared with the ‘low’ category.

It is recommended that review authors do not combine studies at ‘low’ and ‘unclear’ risk of bias in analyses, unless they provide specific reasons for believing that these studies are likely to have been conducted in a manner that avoided bias. In the rest of this section, we will assume that studies assessed as at low risk of bias will be treated as a separate category.

8.8.2.3 Meta-regression and comparisons of subgroups

Formal comparisons of intervention effects according to risk of bias can be done using meta-regression (see Chapter 9, Section 9.6.4). For studies with dichotomous outcomes, results of meta-regression analyses are most usefully expressed as ratios of odds ratios (or risk ratios) comparing results of studies at high or unclear risk of bias with those of studies at a low risk of bias.

$$\text{Ratio of odds ratios} = \frac{\text{Intervention odds ratio in studies at high or unclear risk of bias}}{\text{Intervention odds ratio in studies at low risk of bias}}$$

Alternatively, separate comparisons of high versus low and unclear versus low can be made. For studies with continuous outcomes (e.g. blood pressure), intervention effects are expressed as mean differences between intervention groups, and results of meta-regression analyses correspond to differences of mean differences.

If the estimated effect of the intervention is the same in studies at high and unclear risk of bias as in studies at low risk of bias then the ratio of odds ratios (or risk ratios) equals 1, while the difference between mean differences will equal zero. As explained in Section 8.2.3, empirical evidence from collections of meta-analyses assembled in meta-epidemiological studies suggests that, on average, intervention effect estimates tend to be exaggerated in studies at high or unclear risk of bias compared with studies at a low risk of bias.

When a meta-analysis includes many studies, meta-regression analyses can include more than one domain (e.g. both allocation concealment and blinding).

Results of meta-regression analyses include a confidence interval for the ratio of odds ratios, and a P value for the null hypothesis that there is no difference between the results of studies at high or unclear and low risk of bias. As meta-analyses usually contain a small number of studies, usually the ratio of odds ratios is estimated imprecisely. It is therefore important not to conclude, on the basis of a non-significant P value, that there is no difference between the results of studies at high or unclear and low risk of bias, and therefore no impact of bias on the results. Examining the confidence interval will often show that the difference between studies at high or unclear and low risk of bias is consistent with both no bias and a substantial effect of bias.

A test for differences across subgroups provides an alternative to meta-regression for examination of a single entry (e.g. comparing studies with adequate versus inadequate allocation concealment). Within a fixed-effect meta-analysis framework, such tests are available in RevMan 5. However, such P values are of limited use without corresponding confidence intervals, and in any case the P values will be too small in the presence of heterogeneity within, or between, subgroups.

8.8.3 Including 'Risk of bias' assessments in analyses

Broadly speaking, studies at high or unclear risk of bias should be given reduced weight in meta-analyses, compared with studies at a low risk of bias (Spiegelhalter 2003). However, formal statistical methods to combine the results of studies at high and low risk of bias are not sufficiently well developed that they can currently be recommended for use in Cochrane Reviews (see Section 8.8.4.2). Therefore, the most frequently used approach to incorporating 'Risk of bias' assessments in Cochrane Reviews is to **restrict** meta-analyses to studies at a low (or lower) risk of bias, or to **stratify** studies according to risk of bias.

8.8.3.1 Possible analysis strategies

When risks of bias vary across studies in a meta-analysis, three broad strategies are available for choosing which result to present as the main finding for a particular outcome (for instance, when deciding which result to present in the Abstract). The intended strategy should be described in the protocol for the review.

1. Primary analysis restricted to studies at low (or low and unclear) risk of bias

The first approach involves defining a threshold, based on key bias domains (see Section 8.7) such that only studies meeting specific criteria are included in the primary analysis. The threshold may be determined using the original review eligibility criteria, or using reasoned argument (which may draw on empirical evidence of bias from meta-epidemiological studies). In rare cases, within-meta-analysis comparisons of studies at high and low risk of bias may produce evidence of differences between intervention effect estimates and justify restricting analyses to studies at a low risk of bias (see Section 8.8.2.3). If the primary analysis includes studies at an unclear risk of bias, review authors should justify this choice. Ideally the threshold, or the method for determining it, should be specified in the review protocol. Authors should keep in mind that all thresholds are arbitrary, and that, in theory, studies may lie anywhere on the spectrum from 'free of bias' to 'undoubtedly biased'. The higher the threshold, the more similar the studies will be in their risks of bias, but they may end up being few in number. Review authors who restrict their primary analysis in this way are encouraged to perform **sensitivity analyses** to show how conclusions might be affected if studies at a high risk of bias were included.

2. Present multiple (stratified) analyses

Stratifying according to the summary risk of bias may produce at least three estimates of the intervention effect: from studies at high and low risks of bias and from all studies. Two or more such estimates might be presented with equal prominence, for example, one including all studies and one including only those at a low risk of bias. This avoids the need to make a difficult decision, but may be confusing for readers. In particular, people who

need to make a decision usually require a single estimate of effect. Furthermore, usually 'Summary of findings' tables will present only a single result for each outcome. On the other hand, a stratified forest plot presents all the information transparently.

The choice between strategies 1 and 2 should be based on the context of the particular review and the balance between the potential for bias and the loss of precision when studies at a high or unclear risk of bias are excluded. As explained in Section 8.8.2.3, lack of a statistically significant difference between studies at a high and low risk of bias should not be interpreted as implying an absence of bias, because meta-regression analyses typically have low power.

3. Present all studies and provide a narrative discussion of risk of bias

The simplest approach to incorporating bias assessments in results is to present an estimated intervention effect based on all available studies, together with a description of the risk of bias in individual domains, or a description of the summary risk of bias, across studies. This is the only feasible option when all studies are at a high risk, all are at an unclear risk, or all are at low risk of bias. However, when studies have different risks of bias, we discourage such an approach for two reasons. Firstly, detailed descriptions of risk of bias in the 'Results' section, together with a cautious interpretation in the 'Discussion' section, will often be lost in the 'Authors' conclusions', 'Abstract' and 'Summary of findings' table, so that the final interpretation ignores the risk of bias and decisions continue to be based, at least in part, on flawed evidence. Secondly, such an analysis fails to down-weight studies at a high risk of bias and so will lead to an overall intervention that is too precise, as well as being potentially biased.

When the primary analysis is based on all studies, summary assessments of risk of bias must be incorporated into explicit measures of the quality of evidence for each important outcome, for example using the GRADE system (Guyatt 2008). This can help to ensure that judgements about the risk of bias, as well as other factors affecting the quality of evidence, such as imprecision, heterogeneity and publication bias, are taken into consideration appropriately in interpreting the results of the review (See Chapter 11, Section 11.2).

8.8.4 Other methods for addressing risk of bias

8.8.4.1 Direct weighting

Methods have been described for weighting studies in the meta-analysis according to their validity or risk of bias (Detsky 1992). The usual statistical method for combining results of multiple studies is to weight studies by the amount of information they contribute (more specifically, by the inverse variances of their effect estimates). This gives studies with more precise results (narrower confidence intervals) more weight. It is also possible to weight studies additionally according to validity, so that more valid studies have more influence on the summary result. A combination of inverse variances and validity assessments can be used. The main objection to this approach is that it requires a numerical summary of validity for each study, and there is no empirical basis for determining how much weight to assign to different domains of bias. Furthermore, the resulting weighted average will be biased if some of the studies are biased. Direct weighting of effect estimates by validity or assessments of risk of bias should be avoided (Greenland 2001).

8.8.4.2 Bayesian approaches

Bayesian analyses allow for the incorporation of external information or opinion on the nature of bias (see Chapter 16, Section 16.8; Turner 2009). Prior distributions for specific biases in intervention effect estimates might be based on empirical evidence of bias, on elicited prior opinion of experts, or on reasoned argument. Bayesian methods for adjusting meta-analyses for biases are a subject of current research; currently they are not sufficiently well developed for widespread adoption.

8.9 Random sequence generation

8.9.1 Rationale for concern about bias

Under the domain of random sequence generation in the Cochrane tool for assessing risk of bias, we address whether or not the study used a randomized sequence of assignments. This is the first of two domains in the Cochrane tool that addresses the allocation process, the second being concealment of the allocation sequence (allocation concealment). We start by explaining the distinction between these domains.

The starting point for an unbiased intervention study is the use of a mechanism that ensures that the same sorts of participants receive each intervention. Several interrelated processes need to be considered. Firstly, an allocation sequence must be used that, if perfectly implemented, would balance prognostic factors, on average, evenly across intervention groups. Randomization plays a fundamental role here. It can be argued that other assignment rules, such as alternation (alternating between two interventions) or rotation (cycling through more than two interventions), can achieve the same thing (Hill 1990). However, a theoretically unbiased rule is insufficient to prevent bias in practice. If future assignments can be anticipated, either by predicting them or by knowing them, then selection bias can arise due to the selective enrolment and non-enrolment of participants into a study in the light of the upcoming intervention assignment.

Future assignments may be anticipated for several reasons. These include: 1) knowledge of a deterministic assignment rule, such as by alternation, date of birth or day of admission; 2) knowledge of the sequence of assignments, whether randomized or not (e.g. if a sequence of random assignments is posted on the wall); 3) ability to predict assignments successfully, based on previous assignments (which may sometimes be possible when randomization methods are used that attempt to ensure an exact ratio of allocations to different interventions). Complex interrelationships between theoretical and practical aspects of allocation in intervention studies make the assessment of selection bias challenging. Perhaps the most important practical aspect is concealment of the allocation sequence, that is, the use of mechanisms to prevent foreknowledge of the next assignment. Historically this has been assessed in Cochrane Reviews, with empirical justification. We address allocation sequence concealment as a separate domain in the tool (see Section 8.10).

Randomization allows for the sequence to be unpredictable. An unpredictable sequence, combined with allocation sequence concealment, should be sufficient to prevent selection bias. However, selection bias may arise despite randomization if the random allocations

are not concealed, and selection bias may (in theory at least) arise despite allocation sequence concealment if the underlying sequence is not random. We acknowledge that a randomized sequence is not always completely unpredictable, even if mechanisms for allocation concealment are in place. This may sometimes be the case, for example, if blocked randomization is used, and all allocations are known after enrolment. We do not consider this special situation under either sequence generation or allocation concealment, but address it as a separate consideration in Section 8.15.1.3.

Methodological studies have assessed the importance of sequence generation, including several that have avoided confounding by disease or intervention, which is critical to the assessment (Schulz 1995a, Moher 1998, Kjaergard 2001, Siersma 2007). The BRANDO (Bias in Randomized and Observational Studies) project, which combined data from all available meta-epidemiologic studies, included a reanalysis of 112 meta-analyses from multiple methodological studies that indicated an average exaggeration of 11% in studies with inadequate or unclear sequence generation (relative odds ratio 0.8; 95% confidence interval (CI) 0.82 to 0.96; (Savovic 2012a). In one study, which restricted the analysis to 79 trials that had reported an adequately concealed **allocation sequence**, trials with inadequate **sequence generation** yielded exaggerated estimates of intervention effects, on average, when compared against trials with adequate sequence generation (relative odds ratio of 0.75; 95% CI 0.55 to 1.02; P = 0.07). These results suggest that, if assignments are non-random, some deciphering of the sequence can occur, even with apparently adequate concealment of the allocation sequence (Schulz 1995a).

8.9.2 Assessing risk of bias in relation to adequate or inadequate random sequence generation

Sequence generation is often improperly addressed in the design and implementation phases of randomized controlled trials, and is often neglected in published reports, which causes major problems when assessing the risk of bias. The following considerations may help review authors assess whether sequence generation is suitable to protect against bias, when using the Cochrane tool (Section 8.5).

8.9.2.1 Adequate methods of sequence generation

The use of a random component should be sufficient for adequate sequence generation.

When randomization is used, without constraints, to generate an allocation sequence it is called **simple randomization** or **unrestricted randomization**. In principle, this could be achieved by allocating interventions using methods such as repeated coin-tossing, throwing dice or dealing previously shuffled cards (Schulz 2002a, Schulz 2006). More usually it is achieved by referring to a published list of random numbers, or to a list of random assignments generated by a computer. In trials using large samples (usually meaning at least 100 in each randomized group (Schulz 2002a, Schulz 2002b, Schulz 2006), simple randomization generates comparison groups of relatively similar sizes. In trials that use small samples, simple randomization will sometimes result in an allocation sequence that leads to groups that differ, by chance, quite substantially in size or in the occurrence of prognostic factors (i.e. 'case-mix' variation; Altman 1999).

Example (of low risk of bias): We generated the two comparison groups using simple randomization, with an equal allocation ratio, by referring to a table of random numbers.

Sometimes **restricted randomization** is used to generate a sequence to ensure particular allocation ratios to the intervention groups (e.g. 1:1). Blocked randomization (random permuted blocks) is a common form of restricted randomization (Schulz 2002a, Schulz 2006). Blocking ensures that the numbers of participants to be assigned to each of the comparison groups will be balanced within blocks of, for example, five in one group and five in the other for every 10 consecutively entered participants. The block size may be randomly varied to reduce the likelihood of foreknowledge of intervention assignment.

Example (of low risk of bias): We used blocked randomization to form the allocation list for the two comparison groups. We used a computer random number generator to select random permuted blocks with a block size of eight and an equal allocation ratio.

Stratified randomization is also common; in this, restricted randomization is performed separately within strata. This generates separate randomization schedules for subsets of participants defined by potentially important prognostic factors, such as disease severity and study centres. If simple (rather than restricted) randomization were used in each stratum, then stratification would have no effect, but the randomization would still be valid. Risk of bias may be judged in the same way whether or not a trial claims to have used stratification.

Another approach that incorporates both the general concepts of stratification and restricted randomization is minimization, which can be used to make small groups closely similar for several characteristics. Use of minimization should not automatically be considered as putting a study at risk of bias. However, some methodologists remain cautious about the acceptability of minimization, particularly when it is used without any random component, while others consider it to be very attractive (Brown 2005).

Other adequate types of randomization that are sometimes used include biased coin or urn randomization, replacement randomization, mixed randomization, and maximal randomization (Schulz 2002a, Schulz 2002b, Berger 2003). If these or other approaches are encountered, consultation with a statistician may be necessary.

8.9.2.2 Inadequate methods of sequence generation

Systematic methods, such as alternation, assignment based on date of birth, case record number and date of presentation, are sometimes referred to as 'quasi-random'.

Alternation (or rotation, for more than two intervention groups) might in principle result in similar groups, but many other systematic methods of sequence generation may not. For example, the day on which a patient is admitted to hospital is not solely a matter of chance.

An important weakness with all systematic methods is that concealment of the allocation schedule is usually impossible; this allows foreknowledge of intervention assignment among those recruiting participants to the study, and biased allocations (see Section 8.10).

Example (of high risk of bias): We allocated patients to the intervention group based on the week of the month.

Example (of high risk of bias): Patients born on even days were assigned to Intervention A and patients born on odd days were assigned to Intervention B.

8.9.2.3 Methods of sequence generation with unclear risk of bias

A simple statement such as ‘we randomly allocated’ or ‘using a randomized design’ is often insufficient to be confident that the allocation sequence was genuinely randomized. It is not uncommon for authors to use the term ‘randomized’ even when it is not justified: many trials with declared systematic allocation are described by the authors as randomized. If there is doubt, then the adequacy of sequence generation should be considered to be unclear.

Sometimes trial authors provide some information, but they define their approach incompletely and do not confirm some random component in the process. For example, authors may state that blocked randomization was used, but the process for selecting the blocks, such as a random number table or a computer random number generator, may not be specified. The adequacy of sequence generation should then be classified as unclear.

8.10 Allocation sequence concealment

8.10.1 Rationale for concern about bias

Randomized sequence generation is a necessary, but not a sufficient, safeguard against bias in intervention allocation. Efforts made to generate unpredictable and unbiased sequences are likely to be ineffective if those sequences are not protected by adequate concealment of the allocation sequence from those involved in the enrolment and assignment of participants.

Knowledge of the next assignment – for example, from a table of random numbers openly posted on a bulletin board – can cause selective enrolment of participants on the basis of prognostic factors. Participants who would have been assigned to an intervention deemed to be ‘inappropriate’ may be rejected. Other participants may be deliberately directed to the ‘appropriate’ intervention, which can often be accomplished by delaying a participant’s entry into the trial until the next appropriate allocation appears. Deciphering of allocation schedules may occur even if concealment was attempted. For example, unsealed allocation envelopes may be opened, while translucent envelopes may be held against a bright light to reveal the contents (Schulz 1995a, Schulz 1995b, Jüni 2001). Personal accounts suggest that many allocation schemes have been deciphered by investigators because the methods of concealment were inadequate (Schulz 1995b).

Avoidance of such selection biases depends on preventing foreknowledge of intervention assignment. Decisions on participants’ eligibility and their decision whether to give informed consent should be made in ignorance of the upcoming assignment. Adequate **concealment of allocation sequence** shields those who admit participants to a study from knowing the upcoming assignments.

Several methodological studies have looked at whether concealment of allocation sequence is associated with magnitude of effect estimates in controlled clinical trials while avoiding confounding by disease or intervention. A pooled analysis of seven methodological studies found that effect estimates from trials with inadequate concealment of allocation or unclear reporting of the technique used for concealment of allocation were on average 18% more ‘beneficial’ than effect estimates from trials with adequate concealment of allocation (95% CI 5% to 29%; (Pildal 2007). The BRANDO project, which combined data from all available meta-epidemiologic studies, included a reanalysis of 146 meta-analyses and observed an exaggeration in intervention effect by an average of 7% (relative odds ratio 0.93; 95% CI 0.87 to 0.99; (Savovic 2012b). There was evidence of a larger impact among meta-analyses with subjectively assessed outcomes (relative odds ratio 0.85), but less impact on objectively assessed outcomes (relative odds ratio 0.97), such as all-cause mortality (relative odds ratio 0.98).

8.10.2 Assessing risk of bias in relation to adequate or inadequate allocation sequence concealment

The following considerations may help review authors assess whether concealment of allocation is sufficient to protect against bias, when using the Cochrane tool (Section 8.5).

Proper concealment of the allocation sequence secures strict implementation of an allocation sequence without foreknowledge of intervention assignments. Methods for allocation concealment refer to techniques used to implement the sequence, **not** to generate it (Schulz 1995a). However, most allocation *sequences* that are deemed inadequate, such as allocation based on day of admission or case record number, cannot be adequately concealed, and so fail on both counts. It is theoretically possible, yet unlikely, that an inadequate sequence is adequately concealed (the person responsible for recruitment and assigned interventions would have to be unaware that the sequence being implemented was inappropriate). However, it is not uncommon for an adequate (i.e. randomized) allocation sequence to be inadequately concealed, for example if the sequence is posted on the staffroom wall.

Some review authors confuse allocation concealment with blinding of allocated interventions. Allocation concealment seeks to prevent selection bias in intervention assignment by protecting the allocation sequence *before and until* assignment, and can always be successfully implemented regardless of the study topic (Schulz 1995a, Jüni 2001). In contrast, blinding seeks to prevent performance and detection bias by protecting the sequence *after* assignment (Jüni 2001, Schulz 2002c), and cannot always be implemented – for example, in trials comparing surgical with medical interventions. Thus, allocation concealment up to the point of assignment of the intervention and blinding after that point address different sources of bias and differ in their feasibility.

The importance of allocation concealment may depend on the extent to which potential participants in the study have different prognoses, whether strong beliefs exist among investigators and participants regarding the benefits or harms of assigned interventions, and whether uncertainty about the interventions is accepted by all people involved (Schulz 1995b). Among the different methods used to conceal allocation, central randomization by a third party is perhaps the most desirable. Methods that use envelopes

are more susceptible to manipulation than other approaches (Schulz 1995a). If investigators use envelopes, they should develop and monitor the allocation process to preserve concealment. In addition to use of sequentially numbered, opaque, sealed envelopes, they should ensure that the envelopes are opened sequentially, and only after the envelope has been irreversibly assigned to the participant.

8.10.2.1 Adequate methods of allocation sequence concealment

Table 8.10.a provides minimal criteria for a judgement of adequate concealment of allocation sequence (column on left) and extended criteria, which provide additional assurance that concealment of the allocation sequence was indeed adequate (column on right).

Examples (of low risk of bias; published descriptions of concealment procedures judged to be adequate, as compiled (Schulz 2002d)):

“ . . . that combined coded numbers with drug allocation. Each block of ten numbers was transmitted from the central office to a person who acted as the randomization authority in each centre. This individual (a pharmacist or a nurse not involved in care of the trial patients and independent of the site investigator) was responsible for allocation, preparation, and accounting of [the] trial infusion. The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h. The nurse infused it into the patient at the appropriate rate. The randomization schedule was thus concealed from all care providers, ward physicians, and other research personnel.” (Bellomo 2000).

“ . . . concealed in sequentially numbered, sealed, opaque envelopes, and kept by the hospital pharmacist of the two centres.” (Smilde 2001).

“ Treatments were centrally assigned on telephone verification of the correctness of inclusion criteria . . . ” (de Gaetano 2001).

“ Glenfield Hospital Pharmacy Department did the randomization, distributed the study agents, and held the trial codes, which were disclosed after the study.” (Brightling 2000).

Table 8.10.a: Minimal and extended criteria for judging concealment of allocation sequence to be adequate (low risk of bias)

Minimal criteria for a judgement of adequate concealment of the allocation sequence	Extended criteria to provide additional assurance
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Central randomization	The central randomization office was remote from patient recruitment centres. Participant details were provided, for example, by phone, fax or email and the allocation sequence was concealed to individuals staffing the randomization office until a participant was irreversibly registered.
Sequentially numbered drug containers	Drug containers prepared by an independent pharmacy were sequentially numbered and opened sequentially. Containers were of identical appearance, tamper-proof and equal in weight.
Sequentially numbered, opaque, sealed envelopes	Envelopes were sequentially numbered and opened sequentially only after participant details were written on the envelope. Pressure sensitive or carbon paper inside the envelope transferred the participant's details to the assignment card. Cardboard or aluminium foil inside the envelope rendered the envelope impermeable to intense light. Envelopes were sealed using tamper-proof security tape.

8.11 Blinding of participants and personnel

8.11.1 Rationale for concern about bias

Several types of people can be blinded in a clinical trial: see Box 8.11.a. The first of the two domains in the tool that specifically address blinding focuses on participants and personnel (healthcare providers). It is highly desirable for blinding of participants and personnel to be separated from blinding of outcome assessors, which is covered in the second blinding-related domain (see Section 8.12). Lack of blinding of participants or healthcare providers could bias the results by affecting the *actual* outcomes of the participants in the trial. This may be due to a lack of expectations in a control group, or due to differential behaviours across intervention groups (for example, differential drop out, differential cross-over to an alternative intervention, or differential administration of cointerventions).

Empirical evidence of bias due to lack of blinding of participants and personnel is not currently available. However, there is evidence for studies described as 'blind' or 'double-

blind', which usually includes blinding of one or both of these groups of people. In empirical studies, lack of blinding in randomized trials has been shown to be associated with more exaggerated estimated intervention effects – by 13% on average – measured as odds ratios (Savovic 2012b). These studies have dealt with a variety of outcomes, some of which were objective. The estimated effect has been observed to be more biased, on average, in trials with more subjective outcomes (Wood 2008). Lack of blinding might also lead to bias caused by additional investigations or cointerventions regardless of the type of outcomes, if these occur differentially across intervention groups.

Blinding can be impossible for at least some people (e.g. most patients receiving surgery). However, such studies can take other measures to reduce the risk of bias, such as treating patients according to a strict protocol to reduce the risk of differential behaviours by patients and healthcare providers. An attempt to blind participants and personnel does not ensure successful blinding in practice. Blinding can be compromised for most interventions. For many blinded drug trials, the side effects of the drugs allow the possible detection of which intervention is being received for some participants, unless the study compares two rather similar interventions, e.g. drugs with similar side effects, or uses an active placebo (Boutron 2006).

In blinded studies, especially placebo-controlled trials, there may be concern about whether the participants were truly blinded (and sometimes also whether those caring for the participants were). Several groups have suggested that it would be sensible to ask trial participants to guess which intervention they have been receiving at the end of the trial (Fergusson 2004, Rees 2005), and some reviews of such reports have been published (Fergusson 2004, Hróbjartsson 2007). Evidence of correct guesses exceeding 50% would seem to suggest that blinding may have been broken, but in fact can simply reflect the patients' experiences in the trial: a good outcome, or a marked side effect, will tend to be more often attributed to an active intervention, and a poor outcome to a placebo (Sackett 2007). It follows that we would expect to see some successful 'guessing' when there is a difference in either efficacy or adverse effects, but none when the interventions have very similar effects, even when the blinding has been preserved. As a consequence, review authors should consider carefully whether to take any notice of the findings of such an exercise.

Box 8.11.a: A note on blinding in clinical trials

In general, blinding (sometimes called masking) refers to the process by which study participants, health providers and investigators, including people assessing outcomes, are kept unaware of intervention allocations after inclusion of participants in the study. Blinding may reduce the risk that knowledge of which intervention was received – rather than the intervention itself – will affect outcomes and assessments of outcomes.

Different types of people can be blinded in a clinical trial (Gøtzsche 1996, Haahr 2006):

- participants (e.g. patients or healthy people);

- healthcare providers/personnel (e.g. the doctors or nurses responsible for care);
- outcome assessors, including primary data collectors (e.g. interview staff responsible for measurement or collection of outcome data) and any secondary assessors (e.g. external outcome adjudication committees);
- data analysts (e.g. statisticians); and
- manuscript writers.

The first two types of people are addressed in the tool under the item 'Blinding of participants and personnel'. The third is addressed by the item 'Blinding of outcome assessment'. The last two are not explicitly covered by the tool.

8.11.2 Assessing risk of bias in relation to adequate or inadequate blinding of participants and personnel

Study reports often describe blinding in broad terms, such as 'double blind'. This term makes it impossible to know who was blinded (Schulz 2002c). Such terms are also used very inconsistently (Devereaux 2001, Boutron 2005, Haahr 2006), and the frequency of explicit reporting of the blinding status of study participants and personnel remains low even in trials published in top journals (Montori 2002), despite recommendations in the CONSORT Statement to be explicit (Schulz 2010). A review of methods used for blinding highlighted the variety of methods used in practice (Boutron 2006). The following considerations may help review authors assess whether any blinding of participants and personnel in a study was likely to be sufficient to protect against bias, when using the Cochrane tool (Section 8.5).

When considering the risk of bias from lack of blinding of participants and personnel it is important to consider specifically:

- who was and was not blinded; and
- risk of bias in actual outcomes due to lack of blinding during the study (e.g. due to cointervention or differential behaviour).

Risk of bias may be high for some outcomes and low for others, even if the same people were unblinded in the study. For example, knowledge of the assigned intervention may impact on behavioural outcomes (such as number of clinic visits), while not impacting on physiological outcomes or mortality. Thus, it is highly desirable for assessments of risk of bias resulting from lack of blinding to be made separately for different outcomes. Rather than assessing risk of bias for each outcome separately, it is often convenient to group outcomes with similar risks of bias (see Section 8.5). For example, there may be a common assessment of risk of bias for all subjective outcomes that is different from a common assessment of blinding for all objective outcomes.

8.12 Blinding of outcome assessment

8.12.1 Rationale for concern about bias

Several types of people can be blinded in a clinical trial: see Box 8.11.a. The second of the two domains in the tool that specifically addresses blinding focuses on blinding of outcome assessors. If people who determine outcome measurements are aware of intervention assignments, bias could be introduced into assessments. Outcome assessments may be made by the participants themselves, by their healthcare providers, or by independent assessors.

Empirical studies have shown that lack of blinding in randomized trials is associated with more exaggerated estimated intervention effects – by 13% on average – measured as odds ratios (Savovic 2012b). These studies have dealt with a variety of outcomes, some of which are objective. The estimated effect has been observed to be more biased, on average, in trials with more subjective outcomes (Wood 2008, Savovic 2012b). Recently, a systematic review of trials with both blinded and non-blinded assessment of the same outcome showed biased effect estimates in unblinded assessment, which, for subjective outcomes, exaggerated the odds ratios by 36% (Hróbjartsson 2012).

All outcome assessments can be influenced by lack of blinding, although there are particular risks of bias with more subjective outcomes (e.g. pain or number of days with a common cold). It is therefore important to consider how subjective or objective an outcome is when considering blinding. The importance of blinding and whether blinding is possible may differ across outcomes within a study.

Blinding of outcome assessment can be impossible (e.g. when patients have received major surgery). However, this does not mean that potential biases can be ignored, and review authors should still assess the risk of bias due to lack of blinding of outcome assessment for all studies in their review.

8.12.2 Assessing risk of bias in relation to adequate or inadequate blinding of outcome assessment

Study reports often describe blinding in broad terms, such as ‘double blind’. This term makes it impossible to know who was blinded (Schulz 2002c). Such terms are also used very inconsistently (Devereaux 2001, Boutron 2005, Haahr 2006), and the frequency of explicit reporting of the blinding status of study participants and personnel remains low even in trials published in top journals (Montori 2002), despite recommendations in the CONSORT Statement to be explicit (Moher 2001). A review of methods used for blinding highlighted the variety of methods used in practice (Boutron 2006). The following considerations may help review authors assess whether any blinding of outcome assessment used in a study was likely to be sufficient to protect against bias, when using the Cochrane tool (Section 8.5).

When considering the risk of bias from lack of blinding of outcome assessment it is important to consider specifically:

- who is assessing the outcome; and

- the risk of bias in the outcome assessment (considering how subjective or objective an outcome is).

Assessors of some outcomes may be blinded, while assessors of other outcomes are not. For example, in a surgical trial in which patients are aware of their own intervention, patient-reported outcomes (e.g. quality of life) would obviously be collected with knowledge of the intervention received, whereas other outcomes, measured by an independent clinician (e.g. physical ability), might be blinded. Furthermore, risk of bias may be high for some outcomes and low for others, even if the same people were unblinded in the study. For example, knowledge of the assigned intervention may impact on patient-reported outcomes (such as level of pain), while not impacting on other outcomes such as mortality. In many circumstances the assessment of total mortality might be considered to be unbiased, even if outcome assessors were aware of intervention assignments. Thus, it is highly desirable for assessments of risk of bias resulting from lack of blinding to be made separately for different outcomes.

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Rather than assessing risk of bias for each outcome separately, it is often convenient to group outcomes with similar risks of bias (see Section 8.5). For example, there may be a common assessment of risk of bias for all subjective outcomes that is different from a common assessment of blinding for all objective outcomes.

8.13 Incomplete outcome data

8.13.1 Rationale for concern about bias

Missing outcome data, due to attrition (drop out of participants) during the study or exclusions from the analysis, raise the possibility that the observed effect estimate is biased. We shall use the term **incomplete outcome data** to refer to both attrition and exclusions. When an individual participant's outcome is not available we shall refer to it as **'missing'**.

Attrition may occur for the following reasons.

- Participants withdraw, or are withdrawn, from the study.
- Participants do not attend an appointment at which outcomes should have been measured.
- Participants attend an appointment but do not provide relevant data.
- Participants fail to complete diaries or questionnaires.
- Participants cannot be located (lost to follow-up).
- The study investigators decide, usually inappropriately, to cease follow-up.
- Data or records are lost, or are unavailable for other reasons.

In addition, some participants may be excluded from analysis for the following reasons.

- Some participants are enrolled in the study, but later found to be ineligible.
- An ‘as-treated’ (or per-protocol) analysis is performed (in which participants are included only if they received the intended intervention in accordance with the protocol; see Section 8.13.2).
- The study analysis excluded some participants for other reasons.

Some exclusions of participants may be justifiable, in which case they need not be considered as leading to missing outcome data (Fergusson 2002). For example, participants who are randomized but are subsequently found not to have been eligible for the trial may be excluded, as long as the discovery of ineligibility could not have been affected by the randomized intervention, and preferably on the basis of decisions made while blinded to assignment. The intention to exclude such participants should be specified before the outcome data are seen.

An intention-to-treat (ITT) analysis is often recommended as the least biased way to estimate intervention effects in randomized trials (Newell 1992): see Chapter 16 (Section 16.2). The principles of ITT analyses are to:

- keep participants in the intervention groups to which they were randomized, regardless of the intervention they actually received;
- measure outcome data on all participants; and
- include all randomized participants in the analysis.

The first principle can always be applied. However, the second is often impossible due to attrition beyond the control of the trialists. Consequently, the third principle of conducting an analysis that includes all participants can only be followed by making assumptions about the missing values. Thus very few trials can perform a true ITT analysis without making imputations (see Section 8.13.2.3), especially when there is extended follow-up. In practice, study authors may describe an analysis as ITT even when some outcome data are missing. The term ‘ITT’ does not have a clear and consistent definition, and it is used inconsistently in study reports (Hollis 1999). Review authors should use the term only to imply all three of the principles outlined above, and should interpret any studies that use the term without clarification with care.

Review authors may also encounter analyses described as ‘modified intention-to-treat’, which usually means that participants were excluded if they did not receive a specified minimum amount of the intended intervention. This term is also used in a variety of ways, so review authors should always seek information about precisely who was included.

Note that it might be possible to conduct analyses that include participants who were excluded by the study authors (**reinclusions**), if the review author considers the reasons for exclusions to be inappropriate and the data are available. Review authors are encouraged to do this when possible and appropriate.

Concerns over bias resulting from incomplete outcome data are driven mainly by theoretical considerations. Several empirical studies have looked at whether various aspects of missing data are associated with the magnitude of effect estimates. Most found no clear evidence of bias (Schulz 1995a, Kjaergard 2001, Balk 2002, Siersma 2007). Tierney 2005 observed a tendency for analyses, conducted after trial authors had excluded participants, to favour the experimental intervention compared with analyses that included all participants. There are notable examples of biased ‘per-protocol’ analyses (Melandar 2003), and a review has found more exaggerated effect estimates from ‘per-protocol’ analyses compared with ‘ITT’ analyses of the same trials (Porta 2007). Interpretation of empirical studies is difficult because exclusions are poorly reported, particularly in the pre-CONSORT era before 1996 (Moher 2001). For example, Schulz 1996 observed that the *apparent* lack of exclusions was associated with more beneficial effect sizes as well as with less likelihood of adequate allocation concealment. Hence, failure to report exclusions in trials in Schulz’s study may have been a marker of poor trial conduct rather than true absence of any exclusions.

Empirical research has also investigated the adequacy with which incomplete outcome data are addressed in reports of trials. One study of 71 trial reports from four general medical journals, concluded that missing data are common and often inadequately handled in the statistical analysis (Wood 2004).

8.13.2 Assessing risk of bias from incomplete outcome data

The risk of bias arising from incomplete outcome data depends on several factors, including the amount and distribution of incomplete outcome data across intervention groups, the reasons for outcomes being missing, the likely difference in outcome between participants with and without data, what the study authors have done to address the problem in their reported analyses, and the clinical context. Therefore it is not possible to formulate a simple rule for judging a study to be at a low or high risk of bias. The following considerations may help review authors assess whether incomplete outcome data could be addressed in a way that protects against bias, when using the Cochrane tool (Section 8.5).

It is often assumed that a high proportion of missing outcomes, or a large difference in these proportions between intervention groups, is the main cause for concern over bias. However, these characteristics on their own are insufficient to introduce bias. Here we elaborate on situations in which an analysis can be judged to be at a low or high risk of bias. It is essential to consider the reasons for outcomes being missing as well as the numbers missing.

Risk of bias may be high for some outcomes (or time points) and low for others. For example, there may be fewer dropouts at one-month follow-up than at two-year follow-up. Thus, it is highly desirable for assessments of risk of bias resulting from incomplete outcome data to be made separately for different outcomes (or time points). Rather than assessing risk of bias for each outcome separately, it is often convenient to group outcomes with similar risks of bias (see Section 8.5). For example, there may be a common assessment of risk of bias for all short-term outcomes that is different from a common assessment of blinding for all long-term outcomes.

8.13.2.1 Low risk of bias due to incomplete outcome data

To conclude that there are no missing outcome data, review authors should be confident that the participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear. As noted in Section 8.13.1, participants randomized but subsequently found not to be eligible need not always be considered as having missing outcome data.

Example (of low risk of bias): “All patients completed the study and there were no losses to follow-up, no treatment withdrawals, no trial group changes and no major adverse events”.

Acceptable reasons for missing data

A healthy person’s decision to move house away from the geographical location of a clinical trial is unlikely to be connected with their subsequent outcome. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable.

For studies reporting time-to-event data, all participants who did not experience the event of interest are considered to be ‘censored’ on the date of their last follow-up (we do not know whether the outcome event occurred after follow-up ended, see Chapter 9, Section 9.2.6). The important consideration for this type of analysis is whether such censoring can be assumed to be unbiased, i.e. that the intervention effect (e.g. assessed by a hazard ratio) in individuals who were censored before the *scheduled* end of follow-up is the same as the hazard ratio in other individuals. In other words, there is no bias if censoring is unrelated to prognosis.

If outcome data are missing in both intervention groups, but reasons for these are both reported and balanced across groups, then important bias would not be expected unless the reasons have different implications in the compared groups. For example, ‘refusal to participate’ may mean unwillingness to exercise in an exercise group, whereas refusal might imply dissatisfaction with the advice not to exercise in the other group. In practice, incomplete reporting of reasons for missing outcomes may prevent review authors from making this assessment.

Potential impact of missing data on effect estimates

The potential impact of missing data on **dichotomous outcomes** depends on the frequency (or risk) of the outcome. For example, if 10% of participants have missing outcomes, then their potential impact on the results is much greater if the risk of the event is 10% than if it is 5%. **Error! Reference source not found.** illustrates the potential impact of observed risks. A and B represent two hypothetical trials of 1000 participants in which 90% of the individuals are observed, and the risk ratio among these 900 observed participants is 1. Furthermore, in both trials we suppose that missing participants in the intervention group have a high risk of event (80%) and those in the control group have a much lower risk (20%). The only difference between trials A and B is the risk among the observed participants. In trial A the risk is 50%, and the impact of the missing data, had they been observed, would be low. In trial B the risk is 10%, and the impact of the same missing data,

had they been observed, would be large. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. In trial A this ratio was 100/450 (0.2), whereas in Study B it was 100/90 (1.1).

The potential impact of missing data on **continuous outcomes** increases with the proportion of participants with missing data. It is also necessary to consider the plausible intervention effect among participants with missing outcomes. Table 8.13.b illustrates the impact of different proportions of missing outcomes. A and B represent two hypothetical trials of 1000 participants in which the difference in mean response between intervention and control among the observed participants is 0. Furthermore, in both trials we suppose that missing participants in the intervention arm have a higher mean and those in the control arm have a lower mean. The only difference between trials A and B is the number of missing participants. In trial A, 90% of participants are observed and 10% missing, and the impact of the missing data on the observed mean difference is low. In trial B, half of the participants are missing, and the impact of the same missing data on the observed mean difference is large.

Table 8.13.a: Potential impact of missing data: dichotomous outcomes

	Number randomized	Risk among observed	Observed data	Hypothetical extreme risks among missing participants	Missing data	Complete data	Risk ratio based on all participants
Study A							
Intervention	500	50%	225/450	80%	40/50	265/500	1.13
Control	500	50%	225/450	20%	10/50	235/500	
Study B							
Intervention	500	10%	45/450	80%	40/50	85/500	1.55
Control	500	10%	45/450	20%	10/50	55/500	

Table 8.13.b: Potential impact of missing data: continuous outcomes

	Number randomized	Number observed	Observed mean	Number missing	Hypothetical extreme mean among missing participants	Overall mean (weighted average)	Mean difference based on all participants
Study A							

Intervention	500	450	10	50	15	10.5	1
Control	500	450	10	50	5	9.5	

Study B

Intervention	500	250	10	250	15	12.5	5
Control	500	250	10	250	5	7.5	

8.13.2.2 High risk of bias due to incomplete outcome data

Unacceptable reasons for missing data

A difference in the proportion of incomplete outcome data across groups is of concern if the availability of outcome data is determined by the participants' true outcomes. For example, if participants with poorer clinical outcomes are more likely to drop out due to adverse effects, and this happens mainly in the experimental group, then the effect estimate will be biased in favour of the experimental intervention. Exclusion of participants due to 'inefficacy' or 'failure to improve' will introduce bias if the numbers excluded are not balanced across intervention groups. Note that a non-significant result of a statistical test for differential missingness does not confirm the absence of bias, especially in small studies.

Example (of high risk of bias): "In a trial of sibutramine versus placebo to treat obesity, 13/35 were withdrawn from the sibutramine group, 7 of these due to lack of efficacy. 25/34 were withdrawn from the placebo group, 17 due to lack of efficacy. An 'intention-to-treat' analysis included only those remaining" (Cuellar 2000) i.e. only nine of 34 in the placebo group.

Even if incomplete outcome data are balanced in numbers across groups, bias can be introduced if the reasons for missing outcomes differ. For example, in a trial of an experimental intervention aimed at smoking cessation it is feasible that a proportion of the control intervention participants could leave the study due to a lack of enthusiasm at receiving nothing novel (and continue to smoke), and that a similar proportion of the experimental intervention group could leave the study due to successful cessation of smoking.

The common approach to dealing with missing outcome data in smoking cessation studies (i.e. to assume that everyone who leaves the study continues to smoke) may therefore not always be free from bias. The example highlights the importance of considering *reasons* for incomplete outcome data when assessing risk of bias. In practice, knowledge of why most participants drop out is often unavailable, although an empirical study has observed that 38 out of 63 trials with missing data provided information on reasons (Wood 2004), and this is likely to improve through the use of the CONSORT Statement (Schulz 2010).

'As-treated' (per-protocol) analyses

Eligible participants should be analysed in the groups to which they were randomized, regardless of the intervention that they actually received. Thus, in a study comparing surgery with radiotherapy for treatment of localized prostate cancer, patients who refused surgery and chose radiotherapy subsequent to randomization should be included in the surgery group for analysis. This is because participants' propensity to change groups may be related to prognosis, in which case switching intervention groups introduces selection bias. Although this is strictly speaking an issue of inappropriate analysis rather than incomplete outcome data, studies in which 'as-treated' analyses are reported should be rated as being at a high risk of bias due to incomplete outcome data, unless the number of switches is too small to make any important difference to the estimated intervention effect.

A similarly inappropriate approach to analysis of a study is to focus only on participants who complied with the protocol. A striking example is provided by a trial of the lipid lowering drug, clofibrate (Coronary Drug Project Research Group 1980). The five-year mortality rate in the 1103 men assigned to clofibrate was 20.0%, and was 20.9% in the 2789 men assigned to placebo ($P = 0.55$). Those who adhered well to the protocol in the clofibrate group had lower five-year mortality rate (15.0%) than those who did not (24.6%). However, a similar difference between 'good adherers' and 'poor adherers' was observed in the placebo group (15.1% versus 28.3%). Thus, adherence was a marker of prognosis rather than modifying the effect of clofibrate. These findings show the serious difficulty of evaluating intervention efficacy in subgroups determined by patient responses to the interventions. As non-receipt of intervention can be more informative than non-availability of outcome data, there is a high risk of bias in analyses restricted to compliers, even with low rates of incomplete data.

8.13.2.3 Attempts to address missing data in reports: imputation

A common, but potentially dangerous, approach to dealing with missing outcome data is to **impute** outcomes and treat them as if they were real measurements (see also Chapter 16, Section 16.2). For example, individuals with missing outcome data might be assigned the mean outcome for their intervention group, or be assigned a treatment success or failure. Such procedures can lead both to serious bias and to confidence intervals that are too narrow. A variant of this, the validity of which is more difficult to assess, is the use of 'last observation carried forward' (LOCF). Here, the most recently observed outcome measure is assumed to hold for all subsequent outcome assessment times (Lachin 2000, Unnebrink 2001). LOCF procedures can also lead to serious bias. For example, in a trial of a drug for a degenerative condition, such as Alzheimer's disease, attrition may be related to side effects of the drug. Since outcomes tend to deteriorate with time, using LOCF will bias the effect estimate in favour of the drug. On the other hand, use of LOCF might be appropriate if most people for whom outcomes are carried forward had a genuine measurement relatively recently.

There is a substantial literature on statistical methods that deal with missing data in a valid manner: see Chapter 16 (Section 16.1). There are relatively few practical applications of these methods in clinical trial reports (Wood 2004). Statistical advice is recommended if review authors encounter their use. A good starting point for learning about them is www.missingdata.org.uk.

8.14 Selective outcome reporting

8.14.1 Rationale for concern about bias

Selective outcome reporting has been defined as the selection of a subset of the original variables recorded, on the basis of the results, for inclusion in publication of trials (Hutton 2000); see also Chapter 10 (Section 10.2.2.5). The particular concern about selective outcome reporting is that statistically non-significant results might be selectively withheld from publication. Until recently, published evidence of selective outcome reporting was limited. There were initially a few case studies. Then a small study of a complete cohort of applications approved by a single Local Research Ethics Committee found that the primary outcome was stated in only six of the protocols for the 15 publications obtained. Eight protocols made some reference to an intended analysis, but seven of the publications did not follow this analysis plan (Hahn 2002). Within-study selective reporting was evident or suspected in several trials included in a review of a cohort of five meta-analyses in the *CDSR* (Williamson 2005a).

Convincing direct empirical evidence for the existence of within-study selective reporting bias comes from several studies that compared protocols to publications (Dwan 2013). In one early study (Chan 2004a), 102 trials with 122 publications and 3736 outcomes were identified. Overall, (a median of) 38% of efficacy and 50% of safety outcomes per parallel group trial were incompletely reported, that is, with insufficient information to be included in a meta-analysis. Statistically significant outcomes had a higher odds of being fully reported when compared with non-significant outcomes, both for efficacy (pooled odds ratio 2.4; 95% CI 1.4 to 4.0) and for harms data (pooled odds ratio 4.7; 95% CI 1.8 to 12). Furthermore, when comparing publications with protocols, 62% of trials had at least one primary outcome that was changed, introduced or omitted. A subsequent study of 48 trials funded by the Canadian Institutes of Health Research found very similar results (Chan 2004b). A third study, involving a retrospective review of 519 trial publications and a follow-up survey of authors, compared the presented results with the outcomes mentioned in the methods section of the same article (Chan 2005). On average, over 20% of the outcomes measured in parallel group trials were incompletely reported. Within trials, such outcomes had a higher odds of being statistically non-significant compared with fully reported outcomes (odds ratio 2.0, 95% CI 1.6 to 2.7 for efficacy outcomes; odds ratio 1.9, 95% CI 1.1 to 3.5 for harm outcomes). These three studies suggest an odds ratio of about 2.4 associated with selective outcome reporting that corresponds, for example, to about 50% of non-significant outcomes being published compared to 72% of significant ones.

In all three of these studies, authors were asked whether there were unpublished outcomes, whether those showed significant differences and why those outcomes had not been published. The most common reasons for non-publication of results were lack of clinical importance or lack of statistical significance. Therefore, meta-analyses excluding unpublished outcomes are likely to overestimate intervention effects. Furthermore, authors commonly failed to mention the existence of unpublished outcomes even when those outcomes had been mentioned in the protocol or publication.

Other studies have found similar results (Ghersi 2006, von Elm 2006). In a different type of study, the effect in meta-analyses was larger when fewer of the available trials contributed data to that meta-analysis (Furukawa 2007). This finding also suggests that results may have been selectively withheld by trialists on the basis of the magnitude of effect. Kirkham and colleagues showed that outcome reporting bias affects the conclusions in a substantial proportion of Cochrane Reviews (Kirkham 2010): the median amount of review outcome data missing for any reason was 10%, whereas 50% or more of the potential data were missing in 70 (25%) reviews. A survey of trialists showed that in almost all trials in which prespecified outcomes had been analysed but not reported, this under-reporting resulted in bias (Smyth 2011). Other researchers have highlighted the value of clinical trials registries to identify selective reporting of outcomes (Mathieu 2009).

Bias associated with selective reporting of different measures of the same characteristic seems likely. In trials of treatments for schizophrenia, an intervention effect has been observed to be more likely when unpublished, rather than published, rating scales were used (Marshall 2000). The authors hypothesized that data from unpublished scales may be less likely to be published when they are not statistically significant or that, following analysis, unfavourable items may have been dropped to create an apparent beneficial effect.

In many systematic reviews, only a few eligible studies can be included in a meta-analysis for a specific outcome because the necessary information is not reported by the other studies. While that outcome may not have been assessed in some studies, there is almost always a risk of biased reporting for some studies. Review authors need to consider whether data for an outcome were collected but not reported, or simply not collected.

Selective reporting of outcomes may arise in several ways, some affecting the study as a whole (point 1 below) and others relating to specific outcomes (points 2 to 5 below):

1. **Selective omission of outcomes from reports:** Only some of the analysed outcomes may be included in the published report. If that choice is made based on the results, in particular the statistical significance, the corresponding meta-analytic estimates are likely to be biased.
2. **Selective choice of data for an outcome:** For a specific outcome there may be different time points at which the outcome has been measured, or there may have been different instruments used to measure the outcome at the same time point (e.g. different scales, or different assessors). For example, in a report of a trial in osteoporosis, there were 12 different data sets to choose from for estimating bone mineral content. The standardized mean difference for these 12 possibilities varied between -0.02 and 1.42 (Gøtzsche 2007). If study authors make choices in relation to such results, then the meta-analytic estimate will be biased.
3. **Selective reporting of analyses using the same data:** There are often several different ways in which an outcome can be analysed. For example, continuous outcomes such as blood pressure reduction might be analysed as a continuous or dichotomous variable, with the further possibility of selecting from multiple cut-points. Another

common analysis choice is between endpoint scores versus changes from baseline (Williamson 2005b). Switching from an intended comparison of final values to a comparison of changes from baseline because of an observed baseline imbalance actually introduces bias rather than removes it (as the study authors may suppose; (Senn 1991, Vickers 2001).

4. **Selective reporting of subsets of the data:** Selective reporting may occur if outcome data can be subdivided, for example selecting subscales of a full measurement scale or a subset of events. For example, fungal infections may be identified at baseline or within a couple of days after randomization or may be referred to as ‘break-through’ fungal infections that are detected some days after randomization, and selection of a subset of these infections may lead to reporting bias (Jørgensen 2007, Jørgensen 2014).
5. **Selective under-reporting of data:** Some outcomes may be reported but with inadequate detail for the data to be included in a meta-analysis. Sometimes this is explicitly related to the result, for example reported only as ‘not significant’ or ‘ $P > 0.05$ ’.

Other forms of selective reporting are not addressed here. These include selected reporting of subgroup analyses or adjusted analyses, and presentation of the first-period results in cross-over trials (Williamson 2005a). Also, descriptions of outcomes as ‘primary’, ‘secondary’, etc. may sometimes be altered retrospectively in the light of the findings (Chan 2004a, Chan 2004b). This issue alone should not generally be of concern to review authors (who do not take note of which outcomes are labelled as such in each study), provided it does not influence which results are published.

8.14.2 Assessing risk of bias from selective reporting of outcomes

Although the possibility of *between-study* publication bias can be examined only by considering a complete set of studies (see Chapter 10), the possibility of *within-study* selective outcome reporting can be examined for each study included in a systematic review. The following considerations may help review authors assess whether outcome reporting is sufficiently complete and transparent to protect against bias using the Cochrane tool (Section 8.5).

Statistical methods to detect within-study selective reporting are, as yet, not well developed. There are, however, other ways of detecting such bias although a thorough assessment is likely to be labour intensive. If the protocol is available, then outcomes in the protocol and published report can be compared. If not, then outcomes listed in the methods section of an article can be compared with those for which results are reported. If non-significant results are mentioned but not reported adequately, bias is likely to occur in a meta-analysis. Further information can also be sought from authors of the study reports, although it should be realized that such information may be unreliable (Chan 2004a).

Some differences between protocol and publication may be explained by legitimate changes to the protocol. Although such changes should be reported in publications, none of the 150 studies in the two samples reported in Chan 2004a and Chan 2004b did so.

Review authors should look hard for evidence of collection by study investigators of a small number of key outcomes that are routinely measured in the area in question, and report which studies report data for these and which do not. Review authors should consider the *reasons* why data might be missing from a meta-analysis (Williamson 2005b). Methods for seeking such evidence are not well-established, but we describe some possible strategies.

A useful first step is to construct a matrix indicating which outcomes were recorded in which studies, for example with rows as studies and columns as outcomes. Complete and incomplete reporting can also be indicated. This matrix will allow review authors to see which studies did not report outcomes reported by most other studies.

PubMed, other major reference databases and the internet should be searched for a study protocol; in rare cases the web address may be given in the study report. Alternatively, and more often in the future as mandatory registration of trials becomes more common, a detailed description of the study may be available in a trial registry. Abstracts of presentations relating to the study may contain information about outcomes not subsequently mentioned in publications. In addition, review authors should examine carefully the methods section of published articles for details of outcomes that were assessed.

Missing information that seems sure to have been recorded is of particular interest. For example, some measurements are expected to appear together, such as systolic and diastolic blood pressure, so if only one is reported we should wonder why. An alternative example is a study reporting the proportion of participants whose change in a continuous variable exceeded some threshold; the investigators must have had access to the raw data and so could have shown the results as mean and standard deviation of the changes. Williamson 2005a gives several examples, including a Cochrane Review in which nine trials reported the outcome of treatment failure but only five reported mortality. Yet since mortality was part of the definition of treatment failure, those data must have been collected in the four trials that did not contribute to the analysis of mortality. Bias was suggested by the marked difference in results for treatment failure for trials with or without separate reporting of mortality.

When there is suspicion of, or direct evidence for, selective outcome reporting it is desirable to ask the study authors for additional information. For example, authors could be asked to supply the study protocol and full information for outcomes that were reported inadequately. In addition, they could be asked to clarify whether outcomes mentioned in the article or protocol, but not reported, were analysed, and if so to supply the data.

It is not generally recommended to try to ‘adjust for’ reporting bias in the main meta-analysis. Sensitivity analysis is a better approach to investigate the possible impact of selective outcome reporting (Hutton 2000, Williamson 2005a).

The assessment of risk of bias due to selective reporting of outcomes should be made for the study as a whole, rather than for each outcome. Although it may be clear for a particular study that some specific outcomes are subject to selective reporting while others are not, we recommend the study-level approach because it is not practical to list all fully reported outcomes in the ‘Risk of bias’ table. The ‘support for judgement’ part of the tool (see Section 8.5.2) should be used to describe the outcomes for which there is particular evidence of selective (or incomplete) reporting. The study-level judgement provides an assessment of the overall susceptibility of the study to selective reporting bias.

8.15 Other potential threats to validity

8.15.1 Rationale for concern about bias

The preceding domains (sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting) relate to important potential sources of bias in clinical studies across all healthcare areas. Beyond these specific domains, however, review authors should be alert for further issues that may raise concerns about the possibility of bias. This seventh domain in the ‘Risk of bias’ assessment tool is a ‘catch-all’ for other such sources of bias. For reviews in some topic areas, there may be additional questions that should be asked of all studies. In particular, some study designs warrant special consideration when they are encountered. If particular study designs are anticipated (e.g. cross-over trials, or types of non-randomized study), additional questions relating to the risk of bias in these types of studies may be posed. Assessing risk of bias in non-randomized studies is addressed in Chapter 13, and risk of bias for cluster-randomized trials, cross-over trials and trials with multiple intervention groups is addressed in Chapter 16. Furthermore, some major, unanticipated, problems with specific studies may be identified during the course of the systematic review or meta-analysis. For example, a trial may have substantial imbalance of participant characteristics at baseline. Several examples are discussed in the sections that follow.

8.15.1.1 Design-specific risks of bias

The principal concern over risk of bias in non-randomized studies is selection bias in the form of differences in types of participants between experimental and control intervention groups. Review authors should refer to the full discussion in Chapter 13 (Section 13.5). The main concerns over risk of bias in cluster-randomized trials are: 1) recruitment bias (differential participant recruitment in clusters for different interventions); 2) baseline imbalance; 3) loss of clusters; 4) incorrect analysis; and 5) comparability with individually randomized trials. The main concerns over risk of bias in cross-over trials are: 1) whether the cross-over design is suitable; 2) whether there is a carry-over effect; 3) whether only first-period data are available; 4) incorrect analysis; and 5) comparability of results with those from parallel-group trials. These are discussed in detail in Chapter 16 (Sections 16.3

and 16.4). Risk of bias in studies with more than two intervention groups is also discussed in Chapter 16 (Section 16.5).

8.15.1.2 Baseline imbalance

Baseline imbalance in factors that are strongly related to outcome measures can cause bias in the intervention effect estimate. This can happen through chance alone, but imbalance may also arise through non-randomized (unconcealed) allocation of interventions. Sometimes trial authors may exclude some randomized individuals, causing imbalance in participant characteristics in the different intervention groups. Sequence generation, lack of allocation concealment or exclusion of participants should each be addressed using the specific entries for these in the tool. If further inexplicable baseline imbalance is observed that is sufficient to lead to important exaggeration of effect estimates, then it should be noted. Tests of baseline imbalance have no value in truly randomized trials, but very small P values could suggest bias in the intervention allocation.

Example (of high risk of bias): A trial of captopril versus a conventional anti-hypertensive had small but highly significant imbalances in height, weight, systolic and diastolic BP: $P = 10^{-4}$ to 10^{-18} (Hansson 1999). Such an imbalance suggests failure of randomization (which was by sealed envelopes) at some centres (Peto 1999).

8.15.1.3 Blocked randomization in unblinded trials

Some combinations of methods for sequence generation, allocation concealment and blinding act together to create a risk of selection bias in the allocation of interventions. One particular combination is the use of blocked randomization in an unblinded trial, or in a blinded trial where the blinding is broken, for example because of characteristic side effects. When blocked randomization is used, and when the assignments are revealed after a person has been recruited into the trial, then it is sometimes possible to predict future assignments. This is particularly the case when blocks are of a fixed size and are not divided across multiple recruitment centres. This ability to predict future assignments can happen even when allocation concealment is adequate according to the criteria suggested in Table 8.5.d (Berger 2005).

8.15.1.4 Differential diagnostic activity

Outcome assessments can be biased despite effective blinding. In particular, increased diagnostic activity could lead to increased diagnosis of true, but harmless, cases of disease. For example, many stomach ulcers give no symptoms and have no clinical relevance, but such cases could be detected more frequently on gastroscopy in patients who receive a drug that causes unspecific stomach discomfort and therefore leads to more gastroscopies. Similarly, if a drug causes diarrhoea, this could lead to more digital rectal examinations, and, therefore, also to the detection of more harmless cases of prostatic cancer. Obviously, assessment of beneficial effects can also become biased through such a mechanism. Interventions may also lead to different diagnostic activity, for example if the experimental intervention is a nurse visiting a patient at home, and the control intervention is no visit.

8.15.1.5 Further examples of potential biases

The following list of other potential sources of bias in a clinical study may aid detection of further problems.

- The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing more benefit).
- There is deviation from the study protocol in a way that does not reflect clinical practice (e.g. post hoc stepping-up of doses to exaggerated levels).
- Prior to randomization, there is administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention.
- There is inappropriate administration of an intervention (or cointervention).
- There is contamination (e.g. participants pooling drugs).
- There is occurrence of ‘null bias’ due to interventions being insufficiently well delivered or overly wide eligibility criteria for participants (Woods 1995).
- An insensitive instrument is used to measure outcomes (which can lead to under-estimation of both beneficial and harmful effects).
- There is selective reporting of subgroups.
- Fraud is identified or suspected.

8.15.1.6 Other issues

In this section we comment on some further issues that have been raised in relation to risk of bias, but for which we are unable to provide definitive guidance at present.

Influence of funders

Inappropriate influence of funders (or, more generally, of people with a vested interest in the results) is often regarded as an important risk of bias. For example, in one empirical study, more than half of the protocols for industry-initiated trials stated that the sponsor either owned the data or needed to approve the manuscript, or both; none of these constraints were stated in any of the trial publications (Gøtzsche 2006). It is important that information about vested interests is collected and presented when relevant. However, review authors should provide this information in the ‘Characteristics of included studies’ table (see Section 11.2.2). The ‘Risk of bias’ table should be used to assess specific aspects of methodology that might be influenced by vested interests and which may lead directly to a risk of bias. Note that some decisions that may be influenced by those with a vested interest, such as choice of a particularly low dose of a comparator drug, should be addressed as a source of heterogeneity rather than through the ‘Risk of bias’ tool, since they do not impact directly on the internal validity of the findings.

Early stopping

There is a debate related to the risk of bias of trials that stop early because of benefit. A systematic review and a meta-epidemiologic study showed that truncated randomized trials were associated with greater effect sizes than trials not stopped early, particularly for trials with small sample size (Montori 2005, Bassler 2010). These results were widely discussed (Goodman 2010), and recommendations relating to this item will be provided in future. Currently, review authors should record systematically whether the trial was stopped early for benefit and report this information in the 'Characteristics of included studies' table.

Single-centre versus multi-centre studies

Recent meta-epidemiologic studies of binary and continuous outcomes showed that intervention effect estimates in single-centre randomized trials were significantly larger than in multi-centre trials even after controlling for sample size (Dechartres 2011, Bafeta 2012). The BRANDO project, which combined data from all available meta-epidemiologic studies (Savovic 2012b), found consistent results for subjective outcomes (relative odds ratio 0.86; 95% CI 0.68 to 1.05). Several reasons may explain these results: small study effect, reporting bias, higher risk of bias in single centre studies, or factors related to the selection of the participants, intervention administration, care providers' expertise, etc. Further studies are needed to explore the role and effect of these different mechanisms. However, information related to the number of centres should be systematically collected and reported in the 'Characteristics of included studies' table.

8.15.2 Assessing risk of bias from other sources

Some general guidelines for determining suitable topics for assessment as 'other sources of bias' are provided here. In particular, suitable topics should constitute potential sources of bias and not sources of imprecision, sources of diversity (heterogeneity) or measures of research quality that are unrelated to bias. The topics covered in this domain of the tool include primarily the examples provided in Section 8.15.1. Beyond these specific issues, however, review authors should be alert for study-specific issues that may raise concerns about the possibility of bias, and should formulate judgements about them under this domain of the tool. The following considerations may help review authors assess whether a study is free of risk of bias from other sources using the Cochrane tool (Section 8.5).

Wherever possible, a review protocol should prespecify any questions to be addressed that would lead to separate entries in the 'Risk of bias' table. For example, if cross-over trials are the usual study design for the question being addressed by the review, then specific questions related to bias in cross-over trials should be formulated in advance.

Issues covered by the 'Risk of bias' tool must be a potential source of bias, and not just a cause of *imprecision* (see Section 8.2), and this applies to aspects that are assessed under this 'other sources of bias' domain. A potential source of bias must be able to change the magnitude of the effect estimate, whereas sources of imprecision affect only the uncertainty in the estimate (i.e. its confidence interval). Potential factors affecting precision of an estimate include technological variability (e.g. measurement error) and observer variability.

As the tool addresses internal biases only, any issue covered by this domain should be a potential source of internal bias, and not a source of *diversity*. Possible causes of diversity include differences in dose of drug, length of follow-up, and characteristics of participants (e.g. age, stage of disease). Studies may select doses that favour the experimental drug over the control drug. For example, old drugs are often overdosed (Safer 2002), or may be given under clearly suboptimal circumstances that do not reflect clinical practice (Jørgensen 2007, Johansen 2014). Alternatively, participants may be chosen selectively for inclusion in a study on the basis of previously demonstrated response to the experimental intervention. It is important that such biased choices are addressed in Cochrane Reviews. Although they may not be covered by the ‘Risk of bias’ tool described in the current chapter, they may sometimes be addressed in the analysis (e.g. by subgroup analysis and meta-regression) and should be considered in the grading and interpretation of evidence in a ‘Summary of findings’ table (see Chapter 11).

Many judgements can be made about the design and conduct of a clinical trial, but not all of them may be associated with bias. Measures of ‘quality’ alone are often strongly associated with aspects that could introduce bias. However, review authors should focus on the mechanisms that lead to bias rather than descriptors of studies that reflect only quality. Some examples of quality indicators that should not be assessed within this domain include criteria related to applicability, generalizability or external validity (including those noted above), criteria related to precision (e.g. sample size or use of a sample size (or power) calculation), reporting standards, and ethical criteria (e.g. whether the study had ethical approval or participants gave informed consent). Such factors may be important, and should be presented in the table of ‘Characteristics of included studies’ or in ‘Additional tables’ (see Chapter 11).

Finally, to avoid double-counting, potential sources of bias should not be included as ‘bias from other sources’ if they are more appropriately covered by earlier domains in the tool. For example, in Alzheimer’s disease, patients deteriorate significantly over time during the trial. Generally, the effects of interventions are small but have appreciable toxicity. Dealing satisfactorily with participant losses is very difficult. Those on the experimental intervention are likely to drop out earlier due to adverse effects or death, and hence the measurements on these people, tending to be earlier in the study, will favour the intervention. It is often difficult to get continued monitoring of these participants in order to carry out an analysis of all randomized participants. This issue, although it might at first seem to be a topic-specific cause of bias, would be more appropriately covered in the ‘Incomplete outcome data’ section.

8.16 Methodological standards for the conduct of new Cochrane Intervention Reviews

No.	Status	Name	Standard	Rationale & elaboration	Handbook sections
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C52	Mandatory	Assessing risk of bias	Assess the risk of bias for each included study. For randomized trials, the Cochrane 'Risk of bias' tool should be used, involving judgements and supports for those judgements across a series of domains of bias, as described in Chapter 8 of the <i>Handbook</i> (version 5 or later).	The risk of bias of every included study in a Cochrane Review must be explicitly considered to determine the extent to which its findings can be believed, noting that risks of bias might vary by outcome. Recommendations for assessing bias in randomized studies included in Cochrane Reviews are now well-established. The new tool – as described in the <i>Handbook</i> – must be used for all randomized trials in new reviews and all newly included randomized trials in updated reviews. This does not prevent other tools being used. The discussions in Chapters 8 and 13 of the <i>Handbook</i> should be used to inform the selection of an appropriate tool for non-randomized studies.	8.2.1 8.5.1 8.9 8.10 8.11 8.12 8.13 8.14 8.15
C53	Mandatory	Assessing risk of bias in duplicate	Use (at least) two people working independently to apply the 'Risk of bias' tool to each included study, and define in advance the process for resolving disagreements.	Duplicating the 'Risk of bias' assessment reduces both the risk of making mistakes and the possibility that assessments are influenced by a single person's biases.	8.3.4
C54	Mandatory	Supporting judgements	Justify judgements of risk of bias (high, low and	Providing support for the judgement makes the process transparent. Items	8.5.2

		ts of risk of bias	unclear) and provide this information in the 'Risk of bias' tables (as 'Support for judgement').	which are judged to be at an unclear risk of bias but without accompanying information supporting the judgment appear as empty cells in the graphical plots based on the 'Risk of bias' tool in the published review.	
C55	Highly desirable	Providing sources of information for 'Risk of bias' assessments	Collect the source of information for each 'Risk of bias' judgement (e.g. quotation, summary of information from a trial report, correspondence with investigator etc.). Where judgements are based on assumptions made on the basis of information provided outside publicly available documents, this should be stated.	Readers, editors and referees should have the opportunity to see for themselves where supports for judgments have been obtained.	8.5.2
C56	Highly desirable	Assessing risk of bias due to lack of blinding for different outcomes	Consider blinding separately for different key outcomes.	The risk of bias due to lack of blinding may be different for different outcomes (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from that for a patient-reported pain scale). When there are multiple outcomes, they should be grouped (e.g. objective versus subjective).	8.5.1 8.11.2 8.12.2

C57	Highly desirable	Assessing completeness of data for different outcomes	Consider the impact of missing data separately for different key outcomes to which an included study contributes data.	Often, considering risk of bias due to incomplete (missing) outcome data, this often cannot reliably be done for the study as a whole. The risk of bias due to missing outcome data may be different for different outcomes. For example, there may be less drop-out for a three-month outcome than for a six-year outcome. When there are multiple outcomes, they should be grouped (e.g. short term versus long term). Judgements should be attempted about which outcomes are thought to be at high or low risk of bias.	8.5.1 8.13.2
C58	Highly desirable	Summarizing risk of bias assessments	Summarize the risk of bias for each key outcome for each study.	This reinforces the link between the characteristics of the study design and their possible impact on the results of the study, and is an important prerequisite for the GRADE approach to assessing the quality of the body of evidence.	8.7
C59	Highly desirable	Addressing risk of bias in the synthesis	Address risk of bias in the synthesis (whether quantitative or non-quantitative). For example, present analyses stratified according to summary risk of bias, or restricted to studies at low risk of bias.	Review authors should consider how study biases affect conclusions. This is useful in determining the strength of conclusions and how future research should be designed and conducted.	8.8.1

C60	Mandatory	Incorporating assessments of risk of bias	<i>If randomized trials have been assessed using one or more tools in addition to the Cochrane 'Risk of bias' tool, use the Cochrane tool as the primary assessment of bias for interpreting results, choosing the primary analysis, and drawing conclusions.</i>	For consistency of approach across Cochrane Reviews, the Cochrane 'Risk of bias' tool should take precedence when two or more tools are used. The Cochrane tool also feeds directly into the GRADE approach for assessing the quality of the body of evidence.	8.8.1
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8.17 Chapter information

Editors: Julian PT Higgins, Douglas G Altman and Jonathan AC Sterne on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group.

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8.18 References

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