

# What's new?

## In the Cochrane Handbook for Systematic Reviews of Interventions

### Version 5 for RevMan 5



Version 3, 11 Oct 2007

The *Cochrane Handbook for Systematic Reviews of Interventions* (the *Handbook*) has been revised substantially. Whilst the majority of guidance to Cochrane review authors is unchanged, the entire document has been updated, much of it re-written, and new topics have been added. The new *Handbook* has a new structure, with 21 chapters divided into three parts.

- **Part 1**, relevant to all reviews, introduces Cochrane reviews, covering their **planning and preparation**, and their **maintenance and updating**, and ends with a **guide to the contents** of a Cochrane review or protocol.
- **Part 2**, relevant to all reviews, provides guidance on preparing reviews, covering **eligibility criteria, searching, collecting data, within-study bias, analyzing data, reporting bias, presenting and interpreting results**.
- **Part 3**, relevant to some reviews only, addresses special topics, including particular considerations in addressing **adverse effects**, meta-analysis with **non-standard study designs** and using **individual participant data**. This part has *new* chapters on incorporating **economic evaluations, non-randomized studies, qualitative research, patient-reported outcomes** in reviews, and reviews in **health promotion and public health**. A final chapter describes the new review type of **Overviews of reviews**.

The *Cochrane Handbook for Systematic Reviews of Interventions* does not cover Cochrane Diagnostic test accuracy reviews.

**In this document we summarize the main changes in the guidance to Cochrane review authors in version 5 of the Cochrane Handbook for Systematic Reviews of Interventions that will be relevant to most Intervention reviews:**

1. **Dates and updates**
2. **Assessing risk of bias in included studies using the new 'Risk of bias' tool**
3. **Figures and appendices**
4. **Summarizing evidence, and its quality, in 'Summary of findings' tables**
5. **New statistical methods in RevMan 5**

## 1. Dates and updates

The guidance on the *regularity* of updating is unchanged. However, a new definition for a **review update** is being introduced. Furthermore, the description of a review as an update is to be separated from the suggestion that the review should be re-read by users of the *Cochrane Database of Systematic Reviews* (CDSR). Here is a summary of the main changes:

### Definitions

- Any change to a Cochrane review is either an **update** or an **amendment**.
- An **update** *must* involve a search for new studies (if any new studies are found, these must be incorporated into the review).
- Any other change to a Cochrane review, and any change to a protocol, is an **amendment**, which could involve a little or a lot of work.
- Some reviews undergo important changes (updates or amendments) that warrant new citations in the CDSR and a new MEDLINE/ISI record (e.g. changes to conclusions, authors or correcting serious errors). We call these **new citation versions**.
- Some new citation versions warrant highlighting in the CDSR (e.g. using a flag) – in particular, those that change their conclusions such that they should be read again. We refer to this special subset of new citation versions as reviews with **conclusions changed**.
- Protocols that undergo important changes (e.g. to authors or inclusion criteria) warrant a new citation version. Protocols that change in such a way that they should be re-read by interested users warrant highlighting in the CDSR (e.g. using a flag). We call these protocols with a **major change**.

### Dates and What's new

- Every review will include a new date on which it was **last assessed as up-to-date**. There will also be a single (unpublished) date for the latest search.
- A **'What's new'** table will summarize recent events in the review's evolution, such as an update, an amendment, a decision that conclusions have changed and incorporation of feedback.
- Older 'What's new' events will be moved to a **History** table.

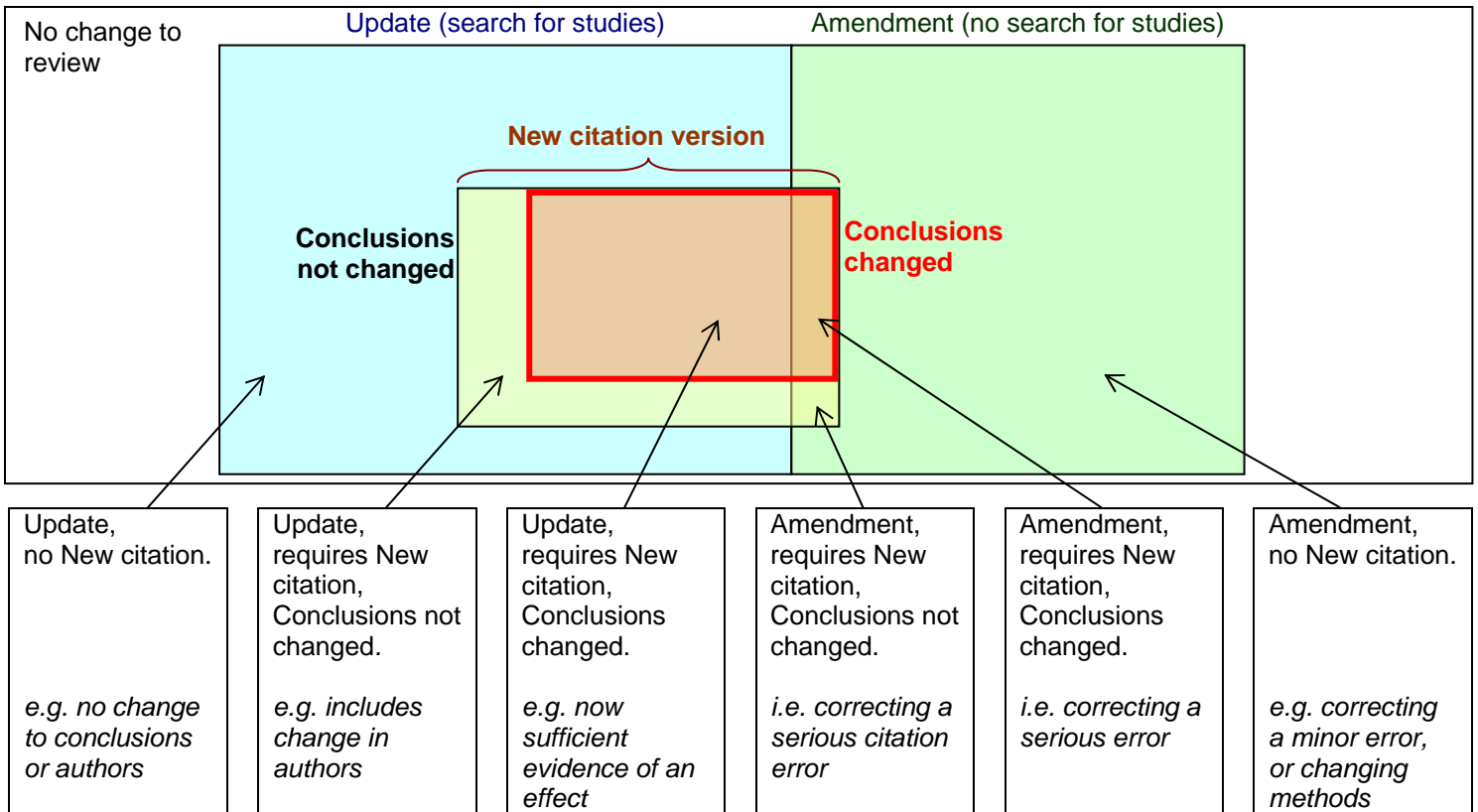
### Flags

- All new protocols, new reviews, updated reviews, reviews with conclusions changed, and protocols with major changes will be identified as such in the CDSR. Amended reviews without conclusions changed will not be flagged.

### More...

- The *Handbook* gives definitions for a review being up-to-date, for new citation versions, for conclusions changed, and for major change to a protocol.
- The Collaboration will no longer use the terms 'substantive update', 'major update', 'minor update', 'major amendment', 'minor amendment', 'major edit' or 'minor edit'. These terms are applied variably and lead to confusion.

**Illustration of concepts of update, amendment, new citation version and conclusions changed for Cochrane reviews**



**2. Assessing risk of bias in included studies using the new 'Risk of bias' tool**

The evaluation of the validity of the included studies is an essential component of a Cochrane review, and this evaluation should also influence the analysis, interpretation and conclusions of the review.

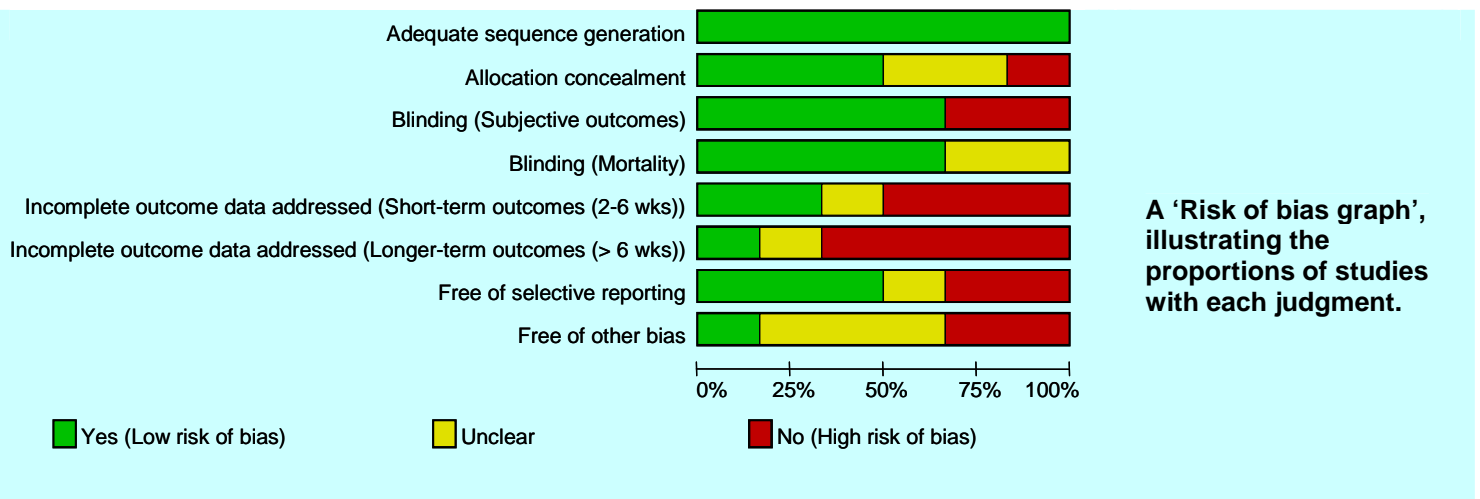
One of the key dimensions in considering whether a study is valid relates to whether it answers its research question 'correctly', that is, in a manner free from bias. This is often described as 'internal validity', or 'quality'. A bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: leading to underestimation or overestimation of the true effect.

Biases can vary in magnitude: some are small (and trivial compared with the true effect) and some are substantial (so that they can completely overwhelm the true effect). It is usually impossible to know to what extent biases have actually affected the results of a particular study and even studies with a methodological flaw might be unbiased. Therefore, building from the research that has shown that particular flaws in the design, conduct and analysis of randomized controlled trials can lead to bias, it is more appropriate to consider **risk of bias** when assessing studies.

Several methods are available to assess or measure the risk of bias, validity or quality of a randomized controlled trial. A new Handbook chapter describes the advantages and disadvantages of available methods for assessing risk of bias, and introduces the Collaboration's new **'risk of bias' tool**. The new tool was developed between 2005 and 2007 by a group of methodologists, editors and review authors. It is a two-part tool, addressing six specific domains, which are discussed in detail in the chapter: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. **(continues...)**

**A 'risk of bias summary' figure**

	Adequate sequence generation	Allocation concealment	Blinding (Subjective outcomes)	Blinding (Mortality)	Incomplete outcome data addressed (Short-term outcomes (2-6 wks))	Incomplete outcome data addressed (Longer-term outcomes (> 6 wks))	Free of selective reporting	Free of other bias
Barry 1988	+	-	+	+	-	-	-	-
Baylis 1989	+	+	+	+	?	?	+	?
Cooper 1987	+	?	-	?	-	-	+	?
Dodd 1985	+	?	+	+	+	-	?	?
Goodwin 1986	+	+	+	+	+	+	+	+
Sanders 1983	+	+	-	?	-	-	-	-



**(...continued)**

A new 'risk of bias' table is included in RevMan 5 as an extension to the 'Characteristics of included studies' table. It is anticipated that review authors will include all six domains listed above in their 'risk of bias' tables. The domain of allocation concealment has been included in earlier versions of RevMan. Existing assessments of allocation concealment (A, B or C) will be imported into a basic 'risk of bias' table.

When completing each of the six domains for a study, review authors will be prompted to provide: (i) a description of what was reported to have happened in the study; and (ii) their judgment on the risk of bias as a consequence of this. This judgement is categorized by using one of the three answers: 'yes', 'no' and 'unclear'. 'Yes' means that there is a low risk of bias and 'no' means that there is a high risk of bias. 'Unclear' is used if there is insufficient information to make this judgement or if the item is not relevant to the study.

The three domains of sequence generation, allocation concealment and selective outcome reporting should each be addressed in the tool by a single item, which would be completed for each study as a whole. For blinding and for incomplete outcome data, review authors might wish to use more than one item per study, because these assessments generally need to be made

separately for different outcomes or different outcome measures.

The final domain ('other sources of bias'), and any other specific domains added by the authors, can be assessed as a single item for studies as a whole (the default in RevMan), or by multiple items.

RevMan 5 enables judgments for each domain to be illustrated in two types of graphics, illustrated above.

To draw conclusions about the overall risk of bias for an outcome, it is necessary to summarize assessments across domains. This involves consideration of the relative importance of different items. Review authors will have to make judgments about which items are most important in their review. For example, for highly subjective outcomes such as pain, authors may decide that blinding of participants is critical and more important than sequence generation.

The new chapter also describes how to incorporate judgments on risk of bias into the analysis, discussion and conclusions for the review. 'Risk of bias' assessments are one component in evaluations of the overall quality of a body of evidence in 'Summary of findings' tables (see later).

### 3. Figures and appendices

**Figures**

Cochrane reviews may include data tables and meta-analyses, created under the 'Comparisons and data' tables in RevMan 4.2. In RevMan 5 they are created under a 'Data and analyses' section.

In future, these tables will be treated as 'supplementary material'. They will continue to be published in full in the CDSR, but versions of reviews may be available that do not include them. Review authors are therefore encouraged to include a small number of forest plots as **figures** within their results section. Authors may also include other types of plots or illustrations as figures. Figures will be included in the main body of the review, so that they are more accessible to users of the review.

Five types of figure can be included in reviews:

- Forest plots (created by RevMan);
- Funnel plots (created by RevMan);
- Risk of bias graphs (created by RevMan);
- Risk of bias summaries (created by RevMan);
- Other figures (created outside of RevMan).

**Appendices**

Appendices can be created in RevMan 5. These are also considered to be supplementary material and might not be included in all versions of the review. They are suitable for such things as:

- Detailed search strategies;
- Detailed statistical methods;
- Data extraction forms.

## 4. Summarizing evidence, and its quality, in 'Summary of findings' tables

The purpose of Cochrane reviews is to facilitate health care decision-making by patients and the general public, clinicians, administrators, and policy makers. A clear statement of the review's findings is essential for this. 'Summary of findings' tables aim to increase the usability of Cochrane reviews and help people make better informed decisions. They provide:

- A list of the most important outcomes, both desirable and undesirable;
- A measure of the typical burden of these outcomes (e.g. typical risk, or typical mean, on control intervention);
- Absolute and relative magnitude of effect (if both are appropriate);
- Numbers of participants and studies addressing these outcomes;
- A summary of the quality of the body of evidence for each of the outcomes.

The assessment of the quality of the body of evidence should make use of the GRADE approach. This awards a grade of 'high', 'moderate', 'low' or 'very low' for each outcome, taking into account:

- Limitations in the design and implementation of available studies (i.e. risk of bias);
- Indirectness of evidence (indirect population, intervention, control, outcomes);
- Unexplained heterogeneity (inconsistency) of results (including problems with subgroup analyses);
- Imprecision of results (wide confidence intervals);
- High probability of reporting bias.

Although not mandatory, review authors are strongly encouraged to include 'Summary of findings' tables in Cochrane reviews, using the specific format described in the *Handbook*. The tables can be prepared using the software program 'GRADEprofiler' and imported into RevMan 5.

## 5. New statistical methods in RevMan 5

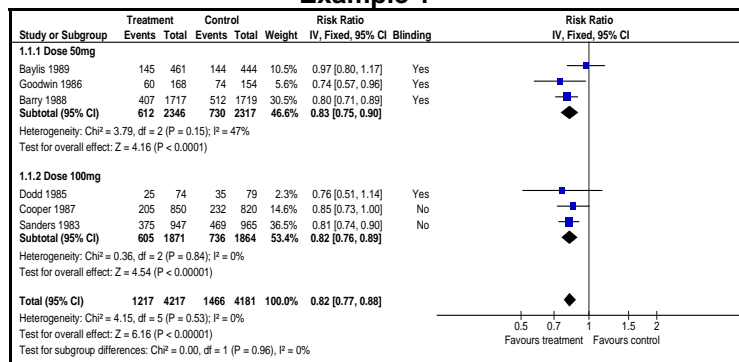
### Methods for dichotomous outcome data

1. An inverse-variance weighted average method has been implemented, providing a further alternative for odds ratios, risk ratios and risk differences. Results may be expected to be very similar to the 'usual' methods. The 'usual' methods, now labelled as 'Mantel-Haenszel' or 'M-H', are still available and are still the default. The new method is labelled as 'I-V'. It allows for simple tests of subgroup differences (see point 3, right), which are not valid in a Mantel-Haenszel framework. See **Example 1**.
2. The focus of the analysis can be swapped from 'events' to 'non-events'. Compared with the analysis focussing on events, this results in 1/OR for odds ratios and in -RD for risk differences. For risk ratios, however, it results in a different summary statistic. See **Example 2**.

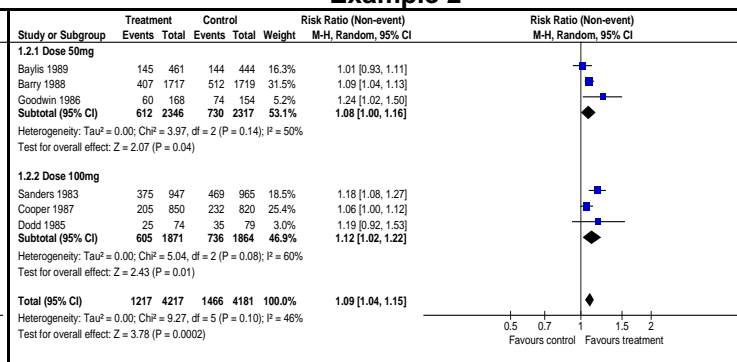
### Heterogeneity statistics

3. In fixed-effect meta-analyses with subgroups, a test for interaction is now included, allowing formal comparison of intervention effects across subgroups. The test is based on heterogeneity  $\chi^2$  (chi-squared) statistics, and assumes intervention effects are equal within subgroups. See **Example 1**.
4. In random-effects meta-analyses, an estimate of the between-study variance ( $\tau^2$ , or 'tau-squared') is now provided at the start of the heterogeneity statistics line. This describes the variation in underlying intervention effects across studies. The statistic can be difficult to interpret, particularly for meta-analyses using odds ratios or risk ratios. However, it may be used informally to determine how much heterogeneity is explained by subgroup differences. See **Example 2**.

Example 1



Example 2



The *Cochrane Handbook for Systematic Reviews of Interventions* is scheduled to be published as a paper-back book by Wiley-Blackwell in late 2008. It will continue to be available for free in electronic form from: <http://www.cochrane.org/resources/handbook>

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