

[Note: the text below is provided for guidance only, you will need to consult the Handbook to adapt the text so that it is suitable for your review. The Handbook is available in the Help menu in RevMan. For some methods you may require statistical support.]

Data collection and analysis

Selection of studies

[Two] review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult **[a third person]**.

Data extraction and management

We will design a form to extract data. For eligible studies, **[at least two]** review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult **[a third person]**. We will enter data into Review Manager software (RevMan 2008) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

[See Handbook sections 8.5a, 8.5.b and 8.5.c]

[Two] review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We will resolve any disagreement by discussion or by involving a **[third]** assessor.

[Note: the following sections refer to individually randomised trials. If cluster-randomised or crossover trials are included appropriate methods for assessing bias in these designs should be used. See Handbook sections 16.3.2 and 16.4.3]

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator),
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;

Note: See Handbook section 8.11.1. Where needed “partial” can be added to the list of options for assessing quality of blinding.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

Note: See Handbook section 8.12.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total

randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

[Note: You may like to specify the level of missing data used to assess that a study is at low risk of bias, for example, a cut-off point of 20% which is the most commonly used value. You may need to specify different levels of missing data that will be assessed as adequate for different outcomes or sets of outcomes. See Handbook section 8.13.]

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

See Handbook section 8.14.2

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We will describe for each included study any important concerns we have about other possible sources of bias.

[Note: Concerns about bias could include for example, was there a potential source of bias related to the specific study design? Was the trial stopped early due to some data-dependent process? Was there extreme baseline imbalance? Has the study been claimed to be fraudulent? See Handbook section 8.15.]

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias *[See table 8.5c in the Handbook]*

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2009). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

[If you combine results from studies in meta-analysis you may need help from a statistician to present and interpret findings from your review. If your review team does not include a statistician, or it is not possible to arrange statistical support locally, contact Sonja Henderson (sonjah@liv.ac.uk) or Frances Kellie (fkellie@liv.ac.uk)].

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

[In some circumstances there may be good reasons for preferring a different statistic; e.g. the Peto odds ratio performs best when the data are very sparse. See section 9.4.4 for a summary of the meta-analysis methods available in RevMan.]

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

[See Handbook section 9.4.5 for a summary of methods for analysing continuous data available in RevMan.]

Unit of analysis issues

[Note: Cluster-randomised trials should be included in your review but special statistical methods are needed to analyse results. If you include such trials you may need to seek statistical advice to prepare data for entry into RevMan. See section 16.3 of the Handbook.]

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their *[sample sizes or standard errors]* using the methods described in the Handbook *[Section 16.3.4 or 16.3.6]* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a

similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a [*sensitivity or subgroup*] analysis to investigate the effects of the randomisation unit.

Crossover Trials

Other unit of analysis issues

[NOTE: It is unlikely that crossover designs will be a valid study design for Pregnancy and Childbirth reviews, and so are expected to be excluded. In the unlikely event that crossover trials are a valid design and included in the review, the Handbook section 16.4 describes methods for risk of bias assessment and analysis. You should describe the methods you plan to use.]

[NOTE: Other unit of analysis issues: Trials in Pregnancy and Childbirth may include outcomes for multiple pregnancies. Special methods are needed to analyse data relating to multiple pregnancies (see the Pregnancy and Childbirth Group Methodological Guidelines and Handbook sections 9.3.7 and 16.3). If your review focuses on multiple pregnancies you will need to describe in your protocol how data will be analysed.]

[NOTE: Other unit of analysis issues: If you are likely to identify trials with more than two treatment groups, special methods are needed to analyse outcome data - see Handbook section 16.4.7. You should describe the methods you plan to use.]

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

[NOTE: It is reasonable to exclude from the analyses data from trials or outcomes that are at high risk of bias, e.g. those with high levels of missing

data or a large number of participants analysed in the wrong group. Criteria for exclusion of data should be specified in the protocol.]

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if I^2 is greater than 30% and either T^2 is greater than zero, or there is a low P-value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

[NOTE: A series of tests to examine funnel plot asymmetry are proposed in the Handbook (Section 10.4.3). If you do not have statistical support available locally, statistical support may be available to assist with the exploration of publication bias and other reporting biases, contact Sonja Henderson (sonjah@liv.ac.uk) or Frances Kellie (fkellie@liv.ac.uk) to ask about this.]

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2008). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses **[list here]**:

1. ...
2. ...

The following outcomes will be used in subgroup analysis: **[list]**

[Note: subgroup analysis will usually be restricted to the review's primary outcomes]

For fixed-effect inverse variance meta-analyses we will assess differences between subgroups by interaction tests. For random-effects and fixed-effects meta-analyses using methods other than inverse variance, we will assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

[Note: Sensitivity analyses should be performed for aspects of the review that might affect the results, for example, where there is risk of bias associated with the quality of some of the included trials. You may also like to carry out sensitivity analysis to explore the effects of fixed- or random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made such as the value of the ICC used for cluster-randomised trials. See section 9.7 of the Handbook]

REFERENCES TO BE ADDED TO REVMAN AND LINKED TO TEXT WHERE APPROPRIATE

Other references

Additional references

Egger 1997

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;25:3443-57.

Higgins 2009

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.2 [updated September 2009]. The Cochrane Collaboration 2009. Available from www.cochrane-handbook.org.

RevMan 2008

Review Manager (RevMan) Version 5.0 for Windows [Computer program].
Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration,
2008.