Model Review (Version 1.0): for PREVENTION: [Intervention] for prevention of [health problem] in [population] *or* for TREATMENT: [Intervention or intervention contrast] for [health problem] in [population]

Review information

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What's new

Date	Event	Description
22 September 2009	Amended	The 'What's new' section should describe the changes to the protocol or review since it was last published in the *CDSR*. At each update or amendment of a review, at least one 'What's new' event should be recorded, containing the type of event, the date of the change and a description of what was changed. This description might be, for example, a brief summary of how much new information has been added to the review (for example, number of studies, participants or extra analyses) and any important changes to the conclusions, results or methods of the review. Entries from the 'What's new' table that do not relate to the current citation version of the review should be listed in the 'History' table. Guidance for completion of the "What's new" section is provided in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 3 Section 5.b).

History

Date	Event	Description

Abstract

Background

The abstract is written when the review is finished. It is *not* part of the protocol stage.

The abstract should be brief (not more than 400 words) and should be organized using the headings below (Background, Objectives, Search strategy, Selection criteria, Data collection and analyses, Results and Author's Conclusions). Abstracts to Cochrane reviews are published in MEDLINE and the Science Citation Index and are made freely available on the internet. It is therefore important that the abstract can be read as a stand-alone document.

Guidelines regarding the abstract can be found in the Cochane Handbook for Systematic Reviews of Intervention
(Chapter 4 Section 3).

Information to include under each abstract heading:

In this section, include a very brief **"Background"** that introduces the major issues regarding

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the review.

Objectives

Brief statement of the primary objectives of the review.

Search strategy

Briefly note search strategy, the databases searched, the dates of the searches, without including MeSH terms.

Selection criteria

Include randomised and quasi-randomised controlled trials relevant to the subject. Discuss cross-over trials and cluster designs if appropriate.

Data collection and analysis

Describe how data were extracted (independent reviewers, number of reviewers). Note whether or not authors were contacted regarding missing data. Include the types of data points (short-term, long-term and, in certain cases, specific discussion of the primary data points and secondary data points). For analyses of categorical data, use relative risk (RR), risk difference (RD) and the number needed to treat (NNT). For continuous data, use weighted mean difference (WMD). Report the 95% confidence interval (CI) on all estimates.

Main results

Note the number of trials included in the review. Report first on the primary outcome of interest and include the typical relative risk and typical risk difference of any meta-analyses performed regarding the primary outcome. For statistically significant outcomes discuss the number needed to treat (NNT). Then discuss the secondary outcomes. If a significant result was noted, these results should be specifically stated in the main results.

Authors' conclusions

Briefly summarise the results from the systematic overview and state the impact on clinical care and the potential for future studies.

Plain language summary

A restatement of the review title using plain language terms.

The plain language summary summarizes the review in a straightforward style that can be understood by consumers of healthcare. Plain language summaries are made freely available on the internet, so these summaries will often be read as stand-alone documents. Plain language summaries have two parts: a plain language title (a restatement of the review's title using plain language terms) and a summary text of not more than 400 words.

Guidance for the content of a plain language summary is provided in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 11).

Background

The background should address the context, help set the rationale for the review, and explain why the questions being asked are important. The choice of clinical outcomes, the rationale for any planned subgroup analyses should be justified.

The full reference for each report cited in the text of the review should be placed in the *Additional references* section unless it is a citation for a study which belongs in the included, excluded, waiting assessment or ongoing studies reference section. All references cited in the

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text should be linked to that reference.

Description of the condition

The review should begin with a brief description of the condition being addressed and its significance. It may include information about the biology, diagnosis, prognosis and public health importance (including prevalence or incidence).

Description of the intervention

The description of the experimental intervention(s) should place the intervention in the context of any standard or alternative interventions. The role of the comparator intervention(s) in standard practice should be made clear. For drugs, basic information on clinical pharmacology should be presented where available. This information might include dose range, metabolism, selective effects, half-life, duration and any known interactions with other drugs. For more complex interventions, a description of the main components should be provided.

How the intervention might work

This section should describe the theoretical reasons why the interventions under review may have an impact on potential recipients; for example, by relating a drug intervention to the biology of the condition. Authors may refer to a body of empirical evidence, such as similar interventions having an impact or identical interventions having an impact on other populations. Authors may also refer to a body of literature that justifies the possibility of effectiveness.

Why it is important to do this review

The background should clearly state the rationale for the review and should explain why the questions being asked are important. It might also mention why this review was undertaken and how it might relate to a wider review of the general problem. If this version of the review is an update of an earlier one, it is helpful to explicitly state this. For example “This is an update of a Cochrane review first published in year X, and previously updated in year Y”. This may be supplemented with a brief description of the main findings of the earlier versions with a statement of any specific reasons there may be for updating the review.

Objectives

The objectives should include a precise statement of the primary objective of the review, ideally in a single sentence. Where possible the style should be of the following form:

“To assess the effects of *[intervention or comparison]* for *[health problem]* for/in *[types of people, disease or problem and setting if specified]*”.

This might be followed by a series of specific objectives relating to different participant groups, different comparisons of interventions or different outcome measures.

In setting objectives, consider what is the main clinical question. If you were designing a trial to answer this question, what would your objectives and outcomes be? What question would a clinician (or public health professional) search for in the Cochrane Library? Do not base your objectives on what published trials have done - base the objectives on what is clinically important.

Specify *a priori* any planned subgroup analyses by subcategories of population, intervention or outcome. Remember, subgroups will depend on your objectives and the rationale for these subgroups will be stated in the background. Include as much detail as possible.

Methods

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Criteria for considering studies for this review

Types of studies

Throughout the section "Criteria for considering studies for this review" use future tense for the protocol and past tense in the completed review.

In the subsection "Types of studies" discuss eligible study designs along with any criteria for inclusion based on the conduct of the studies or their risk of bias. For example, ‘All randomised and quasi-randomised controlled comparisons’ or ‘All randomised controlled trials with blind assessment of outcome’. If cluster or cross-over-designs are anticipated, include them here as being eligible. Note that these designs need integration into several sections of the protocol methods and analysis sections. Exclusion of particular types of randomised studies (for example, cross-over trials) should be justified. Non-randomised studies are not currently supported by the CRNG.

Eligibility criteria for types of study designs are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 5 Section 1.2).

Types of participants

The diseases or conditions of interest should be described here, including any restrictions (for example, diagnoses, age groups and settings). Subgroup analyses should not be listed here (see ‘Subgroup analysis and investigation of heterogeneity’ under ‘Methods’).

Eligibility criteria for types of participants are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 5 Section 2).

Types of interventions

Experimental and comparator interventions should be defined here. Use separate subheadings if appropriate. It should be made clear which comparisons are of interest. Restrictions on dose, frequency, intensity or duration should be stated. Subgroup analyses should not be listed here (see ‘Subgroup analysis and investigation of heterogeneity’ under ‘Methods’).

Eligibility criteria for types of study interventions are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 5 Section 3).

Types of outcome measures

Specify the criteria concerning eligible outcome measures of interest. For each outcome, include when the outcome should be assessed, relevant units, and a definition.

Note that outcome measures do not always form part of the criteria for including studies in a review. If they do not, then this should be made clear. Outcome measures of interest should be listed in this section whether or not they form part of the inclusion criteria.

It is always preferable for the review authors to establish their own outcome criteria and definitions for the review rather than relying on definitions "described by the study authors".

Types of study outcome measures are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 5 Section 4).

Primary outcomes

Primary outcomes should normally reflect at least one potential benefit or one potential area of harm and should be as few as possible. It is normally expected that the review should be able to analyse these outcomes if eligible studies are identified and that the conclusions of the review will be based in large part on the effects of the interventions on these outcomes. Specify *a priori* the criteria concerning eligible outcome measures used to select trials. For

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each outcome, include when the outcome should be assessed, relevant units, and a definition.

Secondary outcomes

Non-primary outcomes should be listed here. For each outcome, include when the outcome should be assessed, relevant units, and a definition.

Search methods for identification of studies

The Methods section in a *protocol* should be written in the future tense. Because Cochrane reviews are updated as new evidence accumulates, methods outlined in the protocol should generally be written as if a suitably large number of studies will be identified to allow the objectives to be met (even if it is known this is not the case at the time of writing).

The Methods section in a *review* should be written in the past tense and should describe what was done to obtain the results and conclusions of the current review. Often a review is unable to implement all of the methods outlined in the protocol, usually because there is insufficient evidence. In such circumstances, it is recommended that the methods that were not implemented be outlined in the section headed 'Differences between protocol and review' (see below) so that it serves as a protocol for future updates of the review.

Search methods are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 6).

Electronic searches

For searches of other electronic databases, state the service provider you used (e.g. PubMed, Ovid) and the electronic databases you searched (e.g. MEDLINE, EMBASE, CINAHL, other) and any constraints. It is best not to restrict the search based on language. The search methods should be described in sufficient detail that the process could be replicated. The databases most likely to be applicable for CNRG reviews are MEDLINE, EMBASE and CINAHL. Depending on the topic, other databases may also be applicable. Depending on the service provider and the database, there are differences in the applicable search terms and syntax. There are differences also in how to limit your search according to age group, study design, and inclusive dates. Thus, the search methods may need to be described separately according to the search provider that was used and the database(s) that was searched.

The full search strategies for each database should be included in an Appendix of the review to avoid interrupting the flow of the text of the review.

Detailed instructions for electronic searches for reviews prepared for the Neonatal Review Group can be found in the document "Overview of Searching Databases for Randomised Trials in Neonatalogy" available on the Cochrane Neonatal web site.

For detecting on-going trials, the CNRG recommends searching the following databases: http://www.controlled-trials.com; http://www.clinicaltrials.gov/.

Search strategies are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 6 Section 4).

Searching other resources

List "grey" literature sources, such as internal reports and conference proceedings. If journals are specifically handsearched for the review, this should be noted but handsearching done by the authors to help build the specialized register of the CRG should not be listed because this is covered in the standardized description of the register. List people (e.g. trialists or topic specialists) and organizations (e.g. granting agencies, industry) who were contacted. List any other sources used, which may include, for example, reference lists, the World Wide Web or

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personal collections of articles. If included, abstracts should present final trial data and provide enough information to assess validity.

Other search resources are discussed in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 6 Section 2).

Data collection and analysis

This section should describe the methods for data collection and analysis.

Guidelines regarding data collection and analysis are discussed in the Cochrane Handbook for Systematic Reviews of Intervention (Chapter 9).

Specific recommendations from the Cochrane Neonatal Review Group for conducting a systematic review are summarised in the document "Preferred meta-analytic Methods in CNRG Reviews".

Selection of studies

Describe the methods used to apply the selection criteria. State whether they were applied independently by more than one review author and how any disagreements are resolved. If relevant, state that you contacted the investigators for additional information or clarification of patient characteristics, details of interventions, definitions of events, additional outcomes, losses to follow-up. If relevant, describe the type of data retrieved and for what trials.

Study selection is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 7 Section 2).

Data extraction and management

Describe the method used to extract or obtain data from published reports or from the original researchers (for example, using a data extraction/data collection form). State whether data were extracted independently by more than one review author and how any disagreements were resolved. If relevant, describe the methods for processing data in preparation for analysis.

For categorical outcomes, define the outcome as the negative outcome (for example death, not survival).

To the extent possible, extract outcome data on all patients randomised.

If outcome data are extracted and presented for other than the number of patients randomised (e.g. only for survivors) build that distinction into the name of the outcome (e.g. cerebral palsy in survivors). Ensure that the outcome is defined consistently with respect to the denominator within each meta-analysis.

Data collection is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 7 Section 6).

Details regarding data entry, construction of comparison tables and options for setting up your analyses graphs can be found in the RevMan Help section of the User Guide (Data and analysis, Construction of table of comparisons).

Assessment of risk of bias in included studies

Describe the methods used to assess risk of bias (or methodological quality) of included studies. State whether methods were applied independently by more than one review author and how any disagreements are resolved. The tool(s) used should be described or referenced, with an indication of how the results are incorporated into the interpretation of the results.

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For purposes of completing the table "Characteristics of included studies", the following criteria should be used: Selection bias (Blinding of randomisation), Performance bias (Blinding of intervention), Attrition bias (Complete follow-up), and Detection bias (Blinding of outcome measurement). Each criterion will be characterized as Yes, Can't tell, No.

In addition, the Risk of bias table will be completed using the following criteria:

1. Sequence generation: Was the allocation sequence adequately generated?

2. Allocation concealment: Was allocation adequately concealed?

3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

4. Incomplete outcome data: Were incomplete outcome data adequately addressed?

5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?

6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Assessing risk of bias is discussed further in the Cochrane Handbook for Systematic Reviews of Intervention (Chapter 8).

Measures of treatment effect

Specific recommendations from the Cochrane Neonatal Review Group for conducting a systematic review are summarised in the document "Preferred meta-analytic Methods in CNRG Reviews".

The effect measures of choice should be stated.

Dichotomous (Catagorical) data: Extract the proportion of randomised participants who experience adverse outcomes (e.g. death, not survival) in the treatment and control groups. Then the event rates will be the adverse event rate, and the relative risk will be the ratio of adverse events in the treated and control groups. A relative risk less than 1 will indicate a benefit in the treatment group as compared to controls. The point estimate will be plotted to the left of a RR of 1, labelled "Favours Treatment" on the graph. A risk difference (Treatment minus Control) which is a negative number will be plotted to the left of RD=0 and labelled "Favours Treatment" on the graph. For significant risk differences it is helpful to report the number needed to treat (NNT) for efficacy and number needed to harm (NNH) for safety outcomes.

For measures of treatment effect use relative risk (RR), relative risk reduction (RR), risk difference (RD) and number needed to treat (1/RD). Relative risk and risk difference are computed by RevMan and should be calculated when appropriate. Relative risk reduction and number needed to treat should be calculated by hand and used in the text of the review when appropriate for discussing the findings. The CNRG does not support using odds ratios for reporting the results of randomised trials. Relative risk (risk ratio) and risk difference are required.

Use 95% confidence intervals for the individual trial results and the typical estimates.

Continuous data

Extract the mean and standard deviation in the treatment and control groups. Check that reported standard deviations (needed by RevMan) are what they purport to be. In original

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papers, SE's are occasionally reported as SD's. If the SD looks very small, be suspicious; you may be able to check by recalculating statistical tests.

Some trials omit SD and se when reporting mean values. The SD can be imputed using the coefficient of variation (CV).

Make sure continuous data are really continuous, e.g. not ordinal or nominal. Nominal, ordinal, interval or ratio data may be collapsed into dichotomies and analysed using categorical methods. Dichotomies should be justified *a priori* as being clinically relevant or biologically important.

A mean difference (Treatment minus Control) which is a negative number will be plotted to the left of MD=0. A negative number may or may not represent a clinical benefit. When it represents a clinical harm, it is necessary to reverse the meta-analysis graph labels "Favors Treatment, Favors Control" (by using the edit option and then the "graph" option).

Effect measures for time-to-event (survival) outcomes (Cochrane Handbook for Systematic Reviews of Intervention Chapter 9 Section 2.6)

If the time to death is of interest, rather than simply the occurrence of death, appropriate analysis is of the time-to-event. An example from neonatology is the time to blockage of a catheter (measured in hours or days). Five options exist for analysis:

i) The outcome may be stated as a binary one by selecting a fixed point of follow-up for analysis and counting the number of neonates with a blocked catheter. For example, after 7 days of follow-up, calculate in each treatment arm how many infants had one or more blocked catheters. This type of data is analysed using relative risk in the usual way. This method ignores important information about the time-to-event.

ii) It is more appropriate to calculate the ***hazard*** of blockage for each treatment group, and the hazard ratio for the comparison between treatments. The ***hazard ratio*** is analysed in meta-view using the relative risk procedure. Proportional hazards, which assume that the risk of the event is constant over the follow-up period, are typically used in this type of analysis. There is no procedure for calculating hazards in meta-view and this statistic should be sought in the original trial report.

iii) If catheter blockage is frequent, the number of blocked catheters per patient can be assessed and analysed as a continuous measure in the usual way. (It would not be appropriate to analyse the total number of all catheters used since these may be removed and exchanged for reasons other than blockage.)

iv) If the time to event is measured as a continuous variable, it is not appropriate to exclude those not experiencing the event. The time to the end of the observation period should be substituted for those not experiencing the event.

v) If multiple blockages are common, it may be possible to average the time to blockage for all catheters used in a single patient, and to compute the mean of means for all patients in that treatment arm. This approach has the advantage of using all the data for each patient.

Unit of analysis issues

Special issues in the analysis of studies with non-standard designs such as cross-over trials and cluster-randomised trials should be described.

Effect Measures for Counts and Rates (Cochrane Handbook for Systematic Reviews of Intervention Chapter 9 Section 2.5)

If a reviewer is contemplating an outcome that may occur more than once to a single patient

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there are three options for analysis. We can use the number of transfusions that may be required by a neonate as an example:

i) The outcome may be stated as a binary one: need for transfusion 0 versus 1+ which would be analysed using relative risk in the usual way.

ii) If the number of transfusions is common and if what is reported is the number of transfusions per infant, the data can be analysed as a continuous measure. "Common" is not readily defined but you may prefer this approach if the trial had more transfusions than patients, i.e. many patients had two or more transfusions.

iii) If transfusions are rare you could calculate the number of transfusions per person-day in each arm. This is equivalent to a person-years analysis. E.g. If there are 30 transfusions in total in 100 participants studied for 14 days each, you have 30/1400 = 0.021 or 2.1 per 100 days. When this is entered for both arms of the trial the rate ratio (relative risk) methodology is used in the usual way. This method is not commonly used because it assumes the risk of events is constant across time and participants. As this is an uncertain assumption in most circumstances, the CNRG does not recommend this approach.

Unit of analysis issues are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 9 Section 3).

Methods for cross-over trials, cluster-randomised trials and other non-standard designs are discussed in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 16).

Dealing with missing data

Strategies for dealing with missing data should be described. This will principally include missing participants due to drop-out (and whether an intention-to-treat analysis will be conducted) and missing statistics (such as standard deviations or correlation coefficients).

Issues relevant to missing data are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 16 Section 1).

Assessment of heterogeneity

Inevitably, studies brought together in a systematic review will differ. Any kind of variability among studies in a systematic review may be termed heterogeneity. It can be helpful to distinguish between different types of heterogeneity. Variability in the participants, interventions and outcomes studied may be described as clinical diversity (sometimes called clinical heterogeneity), and variability in trial design and quality may be described as methodological diversity (sometimes called methodological heterogeneity). Variability in the treatment effects being evaluated in the different trials is known as statistical heterogeneity, and is a consequence of clinical and/or methodological diversity among the studies. Statistical heterogeneity manifests itself in the observed treatment effects being more different from each other than one would expect due to random error (chance) alone.

Approaches to identify, measure and address clinical heterogeneity are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 9 Section 5).

Assessment of reporting biases

Describe how publication bias and other reporting biases are addressed (for example, funnel plots, statistical tests, imputation). Review authors should remember that asymmetric funnel plots are not necessarily caused by publication bias (and that publication bias does not necessarily cause asymmetry in a funnel plot).

Reporting biases are discussed in the Cochane Handbook for Systematic Reviews of

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Intervention (Chapter 10).

Data synthesis

Meta-analysis should be performed using a fixed-effect model. If meta-analyses are not undertaken, systematic approaches to synthesizing the findings of multiple studies should be described.

Meta-analysis and data synthesis are discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 9).

Subgroup analysis and investigation of heterogeneity

All planned subgroup analyses should be listed (or independent variables for meta-regression). Any other methods for investigating heterogeneity of effects should be described.

a) Prespecify, in the protocol, planned subgroup analyses, keep them simple and justify on mechanistic or trial variability grounds.

b) Ensure that subgroups are mutually exclusive

c) Label as such all *a posterior*i subgroup analyses.

d) When subgroup differences are detected, interpret them in light of whether they were proposed a priori, are supported by plausible causal mechanisms, are important (qualitatively vs. quantitatively) and are consistent across studies.

e) We do not propose statistical adjustment for multiple significance testing at this juncture. These procedures are controversial with opinions ranging from “they should never be done” to “always do them”. Some might argue that *a priori* stratification does not need it while *a posteriori* does. Your written commentary should indicate appropriate need for caution when interpreting the results of all subgroup analyses.

Heterogeneity is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 9 Section 5).

Sensitivity analysis

Describe analyses aimed at determining whether conclusions are robust to technical and analytic decisions made during the review process, such as inclusion/exclusion of particular studies from a meta-analysis, imputing missing data or choice of a method for analysis.

a) Test the robustness of the results relative to features of the primary studies and to key assumptions and decisions in your review.

b) Test for bias due to the retrospective nature of systematic review (e.g. with/without trials which meet specified inclusion criteria, methodologic standards, published or unpublished)

c) Consider assessing the fragility of results by determining the effect of small shifts in the number of events between intervention and control groups; i.e. how many additional events would it take to change the statistical or clinical significance of the results in either direction.

d) Consider using cumulative meta-analysis to explore the relationship between effect size and study quality or other relevant features.

Sensitivity analysis is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 9 Section 7).

Results

Description of studies

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Results of the search

The results sections should start with a summary of the results of the search (for example, how many references were retrieved by the electronic searches).

Then write a summary of these trials, in the sections below hi-lighting similarities and differences, rather than a detailed description - which goes in the table of included studies.

Please note, before you enter details in the Tables of Included and Excluded Studies, references to these studies must be added to the appropriate references section (e.g. included studies, excluded studies).

Included studies

Distinguish between studies and reports as there can be more than one report published from a single study.

Each study must be assigned a unique identifier consisting of author, year (e.g. Smith 2000). If Smith was lead author on more than one study published in 2000, the unique identifiers can read Smith 2000a, Smith 2000b.

If a study has more than one report, one of them must be selected as the primary report. The primary report is identified by an asterisk* (selected in the add/edit reference section). Other reports from the same study should be listed under this same unique identifier, i.e. these secondary reports do not get a unique identifier of their own.

It is essential that the number of included studies is clearly stated. This section should comprise a succinct summary of the information contained in the 'Characteristics of included studies' table. An explicit reference to this table should be included. Key characteristics of the included studies should be described, including the study participants, location (e.g. country), setting (if important), interventions, comparisons and outcome measures in the included studies and any important differences among the studies. The sex and age range of participants should be stated here except where their nature is obvious (for example, if all the participants are pregnant). Important details of specific interventions used should be provided (for radiotherapy, for example, this might summarize the total dose, the number of fractions and type of radiation used; for drugs, this might summarize preparation, route of administration, dose and frequency). Review authors should note any other characteristics of the studies that they regard as important for readers of the review to know. The following *optional* subheadings may be helpful: Design; Sample sizes; Setting; Participants; Interventions; and Outcomes.

Table: Characteristics of Included Studies

For each included trial, list the important features of study design and the results of your quality assessments (Methods column), and the clinically important details concerning participants, interventions and outcomes in the table "Characteristics of Included Studies". Use the Notes column to record other features about the trial which are relevant to the review.

In the Intervention column give a brief description of the experimental and control exposures. State (N =) to show the number of subjects randomised to each group; for cross-over trials, state the total number of patients randomised in the trial.

The column Allocation Concealment is meant for rating the quality specifically of allocation concealment in the trial - Adequate = A, Unclear = B, Inadequate = C. This is not meant to put a rating of the quality of the trial as a whole.

'Characteristics of included studies' is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 11 Section 2).

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Excluded studies

This should refer to the information contained in the 'Characteristics of excluded studies' table. An explicit reference to this table should be included. A succinct summary of why studies were excluded from the review should be provided.

The following *optional* headings may be used in the 'Description of studies' section: Ongoing studies; Studies awaiting classification; New studies found at this update; and References to studies excluded from the review.

Give the full reference for each possibly relevant trial that was assessed and then excluded. The editors suggest that if you can decide from the title and abstract that a report which you have retrieved on your search obviously does not describe an eligible trial, you don't have to list it as an excluded trial. On the other hand, if you need to consult the full report before making the decision that it is not eligible, then it should be listed as excluded and the reason given. In any case, you should retain in your files all the references you retrieve from your search, for your own records and also to answer any queries from users.

Table: Characteristics of Excluded Studies

List such studies by study identifier, stating the reason(s) for exclusion.

Risk of bias in included studies

This section should summarize the general risk of bias in results of the included studies, its variability across studies and any important flaws in individual studies. The criteria that were used to assess the risk of bias should be described or referenced under 'Methods' and not here. How each study was rated on each criterion should be reported in a 'risk of bias' table and not described in detail in the text, which should be a concise summary.

'Risk of bias' assessments are addressed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 8 Section 6).

For large reviews, aspects of the risk of bias assessment may be summarized for the primary outcomes under the following headings:

Allocation

A summary of how allocation sequences were generated and attempts to conceal allocation of intervention assignment should be summarized briefly here, along with any judgements concerning the risk of bias that may arise from the methods used.

Blinding

A brief summary of who was blinded or masked during the conduct and analysis of the trial should be reported here. Blinding of outcome assessment should be summarized for each main outcome. Judgements concerning the risk of bias associated with blinding should be summarized.

Incomplete outcome data

The completeness of data should be summarized briefly here for each of the main outcomes. Concerns of the review authors over exclusion of participants and excessive (or differential) drop-out should be reported.

Selective reporting

Concerns over the selective availability of data should be summarized briefly here, including evidence of selective reporting of outcomes, time-points, subgroups or analyses. To identify selective outcome bias, it may be necessary to consult the study protocol from an on-line study

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registration site.

Other potential sources of bias

Any other potential concerns should be summarized here.

Summarise in the text the results of the quality assessments of the included trials (as listed in the Methods column of the Table: Characteristics of Included Studies).

Effects of interventions

It is essential to set up the 'Table of Comparisons' before extracting and analysing data from eligible studies. Detailed instruction on setting up the 'Table of Comparisons' are provided in Appendix 2.

This section should be a summary of the main findings on the effects of the interventions studied in the review. The section should directly address the objectives of the review rather than list the findings of the included studies in turn. The results of individual studies, and any statistical summary of these, should be included in ‘Data and analysis’ tables. Outcomes should normally be addressed in the order in which they are listed under ‘Types of outcome measures'. Subheadings are encouraged if they make understanding easier (for example, for each different participant group, comparison or outcome measure if a review addresses more than one). Any sensitivity analyses that were undertaken should be reported.

In describing the results of the review, organize the text by Comparisons, and under each Comparison, by Outcome. Use headings and subheadings for comparisons and outcomes. To help the reader, follow the same order of comparisons and outcomes and use the same data table numbers (for example, 1.1.1) as in your Table of Comparisons, so that the text matches the order of the outcome data tables. Any pre-specified comparisons or outcomes that could not be analysed or for any planned subgroup analyses that could not be undertaken (in each case because of lack of data from eligible studies) represents a result and should be described as such.

The following plan generally works well:

Within each comparison, describe the results for each major outcome in sequence.

For each outcome, consider presenting:

- the number of trials that assessed that outcome and the total number of subjects included

- the overall proportion of treated and control patients that experienced the event

- whether any individual trials found a significant effect and, if so, which trials

- a quantitative description of the typical effect (meta-analysis result)

For each outcome, consider the result of the meta-analysis in terms of its statistical significance (is the effect real?) and its clinical importance (is the effect large enough to be important?).

Note any important heterogeneity of effect among trials.

Distinguish (and describe as such) any data-driven (*a posteriori*) analyses and results.

Review authors should avoid making inferences in this section. A common mistake to avoid (both in describing the results and in drawing conclusions) is the confusion of ‘no evidence of an effect’ with ‘evidence of no effect’. When there is inconclusive evidence, it is wrong to claim that it shows that an intervention has ‘no effect’ or is ‘no different’ from the control intervention. In this situation, it is safer to report the data, with a confidence interval, as being compatible

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with either a reduction or an increase in the outcome.

Presentation of results is addressed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 11).

Interpretation of numerical results is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 12).

Discussion

Use the structural conventions to guide the discussion section (Docherty 1999; Moher 1999).

Interpretation of numerical results is discussed further in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 12).

Summary of main results

Summarize the main findings (without repeating the 'Effects of interventions' section) and outstanding uncertainties, balancing important benefits against important harms. Refer explicitly to any 'Summary of findings' tables.

Overall completeness and applicability of evidence

Describe the relevance of the evidence to the review question. This should lead to an overall judgement of the external validity of the review. Are the studies identified sufficient to address all of the objectives of the review? Have all relevant types of participants, interventions and outcomes been investigated? Comments on how the results of the review fit into the context of current practice might be included here, although review authors should bear in mind that current practice might vary internationally.

Quality of the evidence

Does the body of evidence identified allow a robust conclusion regarding the objective(s) of the review? Summarize the amount of evidence that has been included (numbers of studies, numbers of participants), state key methodological limitations of the studies, and reiterate the consistency or inconsistency of their results. This should lead to an overall judgement of the internal validity of the results of the review.

Potential biases in the review process

State the strengths and limitations of the review with regard to preventing bias. These may be factors within, or outside, the control of the review authors. The discussion might include the likelihood that all relevant studies were identified, whether all relevant data could be obtained, or whether the methods used (for example, searching, study selection, data extraction, analysis) could have introduced bias.

Agreements and disagreements with other studies or reviews

Comments on how the included studies fit into the context of other evidence might be included here, stating clearly whether the other evidence was systematically reviewed.

Authors' conclusions

Implications for practice

State the major result(s) of the review and the implication(s) for practice. The implications for practice should be as practical and unambiguous as possible. They should not go beyond the evidence that was reviewed and be justifiable by the data presented in the review.

If there is no statistically significant effect, say 'there is no evidence of effect' (not 'there is no

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effect', or the intervention is 'no different' from the control intervention); it is safer to conclude that the data, with a confidence interval, are compatible with either a reduction or an increase in the outcome. Clinical significance as well as statistical significance should be considered.

The conclusions of the systematic review should simply summarise the likely benefits and risks of the intervention. It is not necessary, and often not justified, to go beyond this and make a recommendation for practice. Consider the strength of inference regarding the clinical implications of the results, which varies directly with the comprehensiveness of search for all relevant trials, the methodological quality of the primary trials on which the review was based, and the degree of consistency of results among the trials. For results which have the potential to influence clinical practice, state their potential clinical importance in terms of

- the beneficial effects vs. any unwanted side effects or increased economic costs

- limits of applicability, i.e. in whom the treatment should be considered (e.g. baseline risk for primary outcome above which benefits are likely to outweigh harms).

Implications for research

This section of Cochrane reviews is used increasingly often by people making decisions about future research, and review authors should try to write something that will be useful for this purpose. As with the ‘Implications for practice’, the content should be based on the available evidence and should avoid the use of information that was not included or discussed within the review.

Consider which questions have been well answered (further trials not warranted), which questions remain important because they have not been answered clearly (further trials warranted), and which questions remain important in only certain populations (further trials in selected populations warranted).

Consider hypotheses generated by data-driven (*a posteriori*) analyses which now require testing in future trials.

Consider new questions that arise from the reviewed research (e.g. new interventions, modification of dose, combination of therapies).

It is important that this section is as clear and explicit as possible. General statements that contain little or no specific information, such as “Future research should be better conducted” or “More research is needed” are of little use to people making decisions and should be avoided.

Further guidance on formulating conclusions is provided in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 12 Section 7).

Acknowledgements

This section should be used to acknowledge any people or organizations that the review authors wish to acknowledge including people who are not listed among the authors. This would include any previous authors of the Cochrane review or previous sources of support to the review and might include the contributions of the editorial team of the CRG. Permission should be obtained from persons acknowledged.

Add people or institutions who have contributed to your review. This excludes authors of the review as authorship acknowledges this. It might include people who have provided extra data for some of the studies or people who have helped edit the review.

Contributions of authors

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The contributions of the current co-authors should be described in this section. One review author should be identified as the guarantor of the review. All review authors should discuss and agree on their respective descriptions of contribution before the review is submitted for publication on the *CDSR*. When the review is updated, this section should be checked and revised as necessary to ensure that it is accurate and up to date.

The following potential contributions have been adapted from Yank et al (Yank 1999). This is a suggested scheme and the section should describe what people did, rather than attempt to identify which of these categories someone's contribution falls within. Ideally, the review authors should describe their contribution in their own words:

- Conceiving the review
- Designing the review
- Coordinating the review
- Data collection for the review
- Designing search strategies
- Undertaking searches
- Screening search results
- Organizing retrieval of papers
- Screening retrieved papers against inclusion criteria
- Appraising quality of papers
- Extracting data from papers
- Writing to authors of papers for additional information
- Providing additional data about papers
- Obtaining and screening data on unpublished studies
- Data management for the review
- Entering data into RevMan
- Analysis of data
- Interpretation of data
- Providing a methodological perspective
- Providing a clinical perspective
- Providing a policy perspective
- Providing a consumer perspective
- Writing the review
- Providing general advice on the review
- Securing funding for the review
- Performing previous work that was the foundation of the current review

Declarations of interest

Cochrane reviews should be free of any real or perceived bias introduced by the receipt of any

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benefit in cash or kind, any hospitality, or any subsidy derived from any source that may have or be perceived to have an interest in the outcome of the review. It is a matter of Cochrane Collaboration policy that direct funding from a single source with a vested interested in the results of the review is not acceptable.

Review authors should report any present or past affiliations or other involvement in any organization or entity with an interest in the review that might lead to a real or perceived conflict of interest. Situations that might be perceived by others as being capable of influencing a review author's judgements include personal, political, academic and other possible conflicts, as well as financial conflicts. Review authors must state if they have been involved in a study included in the review.

If there are no known conflicts of interest, this should be stated explicitly, for example, by writing 'None known'.

A summary of the Collaboration's policy on conflicts of interest appears in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 2 Section 6).

Differences between protocol and review

It is sometimes necessary to use different methods from those originally described in the protocol. This could be because:

- Methods for dealing with a particular issue had not been specified in the protocol;
- Methods in the protocol could not be applied (for example, due to insufficient data or a lack of information required to implement the methods);
- Methods are changed because a preferable alternative is discovered.

Some changes of methods from protocol to review are acceptable but must be fully described in this section. The section provides a summary of the main changes in methods for the review over time. It should be used to:

- Point out any methods that were determined subsequent to the most recent published protocol (e.g. adding or changing outcomes; adding 'Risk of bias' or 'Summary of findings' tables);
- Summarize methods from the protocol that could not be implemented in the current review (e.g. because no studies fell in a particular pre-defined subgroup);
- Explain any changes in methods from the protocol to the review, state when they were made and provide the rationale for the changes. Such changes should not be driven by findings on the effects of interventions. Consider the potential effect on the review's conclusions of any changes in methods, and consider sensitivity analyses to assess this.

Published notes

Published notes will appear in the review in the *CDSR*. They may include editorial notes and comments from the CRG, for example where issues highlighted by editors or referees are believed worthy of publication alongside the review. The author or source of these comments should be specified (e.g. from an editor or a referee).

Published notes must be completed for all withdrawn protocols and reviews, giving the reason for withdrawal. Only basic citation information, sources of support and published notes are published for withdrawn protocols and reviews.

Characteristics of studies

Characteristics of included studies

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Instructions

Methods	study design (stating whether or not the study was randomised), including, where relevant, a clear indication of how the study differs from a standard parallel group design (e.g. a cross-over or cluster-randomised design); duration of the study (if not included under Intervention).
Participants	setting; relevant details of health status of participants; age; sex; country. Sufficient information should be provided to allow users of the review to determine the applicability of the study to their population, and to allow exploration of differences in participants across studies.
Interventions	a clear list of the intervention groups included in the study. If feasible, sufficient information should be provided for each intervention to be replicated in practice; for drug interventions, include details of drug name, dose, frequency, mode of administration (if not obvious), duration (if not included under Methods); for non-drug interventions, include relevant considerations and components related to the intervention.
Outcomes	a clear list of either (i) outcomes and time -points from the study that are considered in the review; or (ii) outcomes and time-points measured (or reported) in the study. Study results should not be included here (or elsewhere in this table).
Notes	further comments from the review authors on aspects of the study that are not covered by the categories above. Note that assessments of risk of bias should be made in a 'Risk of bias' table.

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment?	Unclear	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.
Blinding?	Unclear	Describe all measures used, if any, to blind study participants and personnel from knowledge of which

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		intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Incomplete outcome data addressed?	Unclear	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Free of selective reporting?	Unclear	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
Free of other bias?	Unclear	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.

Footnotes

Further guidance on 'Characteristics of included studies' tables is provided in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 11 Section 2).

Further guidance on 'Risk of bias' tables is provided in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 8 Section 5.1).

Characteristics of excluded studies

Footnotes

Studies meeting the inclusion criteria or appearing to meet the inclusion criteria that were excluded should be listed and the reason for exclusion should be given (for example, inappropriate comparator intervention). This should be kept brief and a single reason for exclusion is usually sufficient.

Characteristics of studies awaiting classification

Footnotes

The 'Characteristics of studies awaiting classification' table (formerly 'Studies awaiting assessment') has the same structure as the 'Characteristics of included studies' table. This table should be used for:

- Studies about which an inclusion or exclusion decision cannot be made because sufficient information is not available. All reasonable attempts to obtain information must be made before studies are left here on publication of the review. When information is not available for a table entry, the text 'Not known' should be inserted.

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- Studies that have been identified but are awaiting an update to the review. Studies that have the potential to impact on conclusions, or studies that receive wide publicity, may warrant a mention in the review in the period between updates. An amended review may therefore be produced with such studies briefly summarised in this table. The full update, with such studies fully incorporated, should be completed as soon as possible. When information is not available for a table entry, the text 'Not yet assessed' should be inserted.

Characteristics of ongoing studies

Footnotes

The 'Characteristics of ongoing studies' table has eight entries for each study: Study name, Methods, Participants, Interventions, Outcomes, Starting date, Contact information and Notes. The contents of these entries should be comparable to those in the table of 'Characteristics of included studies'. Footnotes should be used to explain any abbreviations used in the table (these will be published in the *CDSR*).

Summary of findings tables

1 Summary of findings table

A 'Summary of findings' table is an optional means of presenting findings for the most important outcomes, whether or not evidence is available for them. Where appropriate, a 'Summary of findings' table includes a summary of the amount of evidence; typical absolute risks for people receiving experimental and control interventions; estimates of relative effect (e.g. relative risk or odds ratio); a depiction of the quality of the body of evidence; comments; and footnotes. The assessment of the quality of the body of evidence should follow the GRADE framework, which combines considerations of risk of bias, directness, heterogeneity, precision and publication bias.

A full specification and discussion of 'Summary of findings' tables is provided in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 11).

The GRADE system is overviewed in the Cochane Handbook for Systematic Reviews of Intervention (Chapter 12).

Footnotes

Additional tables

1 Additional tables

The Additional tables feature provides a flexible way of creating tables, allowing presentation of results of both trials and meta-analyses, and other meta-analytical investigations (such as meta-regression analyses). Important results from all Additional tables should be summarized in the Results section of the review text.

Additional tables may be used for information that cannot be conveniently placed in the text or in fixed tables. Examples include:

- Information to support the background;
- Summaries of study characteristics (such as detailed descriptions of interventions or outcomes);
- Results that do not fit into 'Data and analysis' tables, for example skewed data reporting a median and range.

Footnotes

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References to studies

Included studies

Instructions

Give the full reference (authors, title of article, journal, year, volume, pages) for each report included. Reference should be in the following style: Smith JA, Jones BA. Title of article. New England Journal of Medicine 2000;155(4):75-8. Check accuracy and formatting of your references using Citation Matcher http://www.ncbi.nlm.nih.gov/PubMed/wgetcit.html. Further guidance on entering references, "Included studies", "Excluded studies", "Studies awaiting classification", "Ongoing studies" and "Other references" are provided in the Cochane Handbook for Systematic Reviews of Intervention, Chapter 4 Section 7.1 http://www.cochrane-handbook.org/ Also refer to Cochrane Style Guide http://www.cochrane.org/style/home.htm.

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Classification pending references

Data and analyses

Figures

Sources of support

Internal sources

- List any internal sources of support that you received, USA

External sources

- List any external sources of support that you received, Canada

Feedback

1 Feedback summary

Summary

There is a formal mechanism on *The Cochrane Library* to facilitate and manage feedback from users of reviews. Feedback, formerly called Comments and Criticisms, is designed to “amend reviews in the light of new evidence to reflect the emergence of new data, valid feedback, solicited or unsolicited, from whatever source” (Chalmers 1994).

Feedback on a review can be received at any time after publication and will be sent to the Feedback editor of the responsible CRG. This editor will ensure that the feedback and language is appropriate and then will pass it on to review authors for response (usually required within one month of sending). When responding to feedback, authors are asked to:

- confine the response to the points made in the feedback;
- reply to every substantive point, explicitly stating whether the author agrees or disagrees

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with the feedback and providing supporting evidence where necessary;
- describe any changes made to the review in response to the feedback; and
- reply in clear and plain language.

Updating a review provides the opportunity to incorporate feedback into the review, addressing valid concerns and adding any additional studies identified through the feedback mechanism.

Reply

Contributors

Appendices

1 Optional tables

Summary of findings tables

[experimental intervention] compared with [control intervention] for [health problem]						
Patient or population: [participants] with [health problem] **Settings:** [setting] **Intervention:** [experimental intervention] **Comparison:** [control intervention]						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk [control]	**Corresponding risk [experimental]**				
[outcome 1] [follow-up]	**Low risk population**		RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
	[value] per 1000	[value] per 1000 ([value] to [value])				
	Medium risk population					
	[value] per 1000	[value] per 1000 ([value] to [value])				
	High risk population					
	[value] per 1000	[value] per 1000 ([value] to [value])				
[outcome 1] [range of scale or scale description] [follow-up]	The mean [outcome] ranged across control groups from [value] [measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] [(value)]	[Delete as appropriate] +OOO very low ++OO low +++O moderate	

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					++++ high	
[outcome 2] [follow-up]	**Low risk population**		RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
	[value] per 1000	[value] per 1000 ([value] to [value])				
	Medium risk population					
	[value] per 1000	[value] per 1000 ([value] to [value])				
	High risk population					
	[value] per 1000	[value] per 1000 ([value] to [value])				
[outcome 2] [range of scale or scale description] [follow-up]	The mean [outcome] ranged across control groups from [value] [measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] [(value)]	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome 3] [follow-up]	**Low risk population**		RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
	[value] per 1000	[value] per 1000 ([value] to [value])				
	Medium risk population					
	[value] per 1000	[value] per 1000 ([value] to [value])				
	High risk population					
	[value] per 1000	[value] per 1000 ([value] to [value])				
[outcome 3] [range of scale or scale	The mean [outcome] ranged across control groups from	The mean [outcome] in the intervention groups was [value] [lower/higher]		[value] [(value)]	[Delete as appropriate] +OOO very low ++OO low	

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description] [follow-up]	[value] [measure]	[(value to value lower/higher)]			+++O moderate ++++ high	
[outcome 4] [follow-up]	**Low risk population** [value] per 1000	[value] per 1000 ([value] to [value]) **Medium risk population** [value] per 1000 ([value] to [value]) **High risk population** [value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome 4] [range of scale or scale description] [follow-up]	The mean [outcome] ranged across control groups from [value] [measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] [(value)]	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome 5] [follow-up]	**Low risk population** [value] per 1000	[value] per 1000 ([value] to [value]) **Medium risk population** [value] per 1000 ([value] to [value]) **High risk population** [value] per 1000 ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome 5] [range of	The mean [outcome] ranged	The mean [outcome] in the intervention			[Delete as appropriate] +OOO very low	

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scale or scale description] [follow-up]	across control groups from [value] [measure]	groups was [value] [lower/higher] [(value to value lower/higher)]		[value] [(value)]	++OO low +++O moderate ++++ high	
[outcome 6] [follow-up]	**Low risk population** [value] per 1000	[value] per 1000 ([value] to [value]) **Medium risk population** [value] per 1000	RR [value] ([value] to [value]) **High risk population** [value] per 1000	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome 6] [range of scale or scale description] [follow-up]	The mean [outcome] ranged across control groups from [value] [measure]	The mean [outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] [(value)]	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome 7] [follow-up]	**Low risk population** [value] per 1000	[value] per 1000 ([value] to [value]) **Medium risk population** [value] per 1000	RR [value] ([value] to [value]) **High risk population** [value] per 1000	[value] ([value])	[Delete as appropriate] +OOO very low ++OO low +++O moderate ++++ high	
[outcome	The mean	The mean			[Delete as appropriate]	

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7] [range of scale or scale description] [follow-up]	[outcome] ranged across control groups from [value] [measure]	[outcome] in the intervention groups was [value] [lower/higher] [(value to value lower/higher)]		[value] [(value)]	+OOO very low ++OO low +++O moderate ++++ high	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk Ratio; [other abbreviations, e.g. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

2 Table of Comparisons Outline

The Table of Comparisons sets out:

1) the comparisons to be made

2) the outcomes under each comparison

3) any subgroup analyses (by subcategories of population, intervention, or outcome)

COMPARISONS

Comparisons can be:

- Between two interventions, for example:

    Treatment vs. Control

    Treatment A vs. Treatment B

- Between two interventions restricted by population or by intervention, for example:

    Treatment vs. Control in Babies < 1500g

    Oral treatment vs. Control

    Intravenous treatment vs. Control

OUTCOMES

- Under each comparison, list the different outcomes

- Outcomes should ideally be assessed and reported among all randomised (intention-to-treat)

- If an outcome is reported among a subset of all randomised, build that distinction into the

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name of the outcome, for example:

Cerebral palsy among survivors at 1 - 3 years

- Competing risks: mutually exclusive outcomes which compete with each other can be listed separately and then aggregated, for example:

Bronchopulmonary dysplasia at 28 days

Death up to 28 days

Bronchopulmonary dysplasia or death at 28 days

- Any outcome can be divided into two or more subcategories (although this is usually not required)

- If subcategories for an outcome are mutually exclusive, the meta-analysis results of the different subcategories can be combined to give an overall result, for example:

Early neonatal deaths (0 - 7 days)

Late neonatal deaths (8 - 28 days)

Total neonatal deaths (0 - 28 days)

- If subcategories for an outcome are not mutually exclusive, or where it does not make sense to compute an overall result, the meta-analysis results of the different subcategories must not be combined to give an overall result, for example "subtotals only" would be chosen for the following subcategories of the outcome, Death

Death before hospital discharge

Neonatal death (< 28 days)

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