Standards for the CONDUCT of new Cochrane Intervention Reviews (C1-C75)

Key points and introduction

Key points:

- **The conduct Standards should be consulted during preparation of the protocol for a Cochrane Intervention Review.**
- **They describe the methods that should be implemented throughout the review process.**
- **Few specific methods are mandatory, one notable exception being the Cochrane tool for assessing risk of bias when randomized trials are included in the review.**

The MECIR Standards for conduct of a Cochrane Intervention Review provide expectations for the general methodological approach to be followed from designing the review up to interpreting the findings at the end. They should be consulted particularly when preparing the protocol for the review. The protocol describes the review question, the criteria for considering studies for the review, and the methods that will be followed to identify, appraise, summarize and synthesize the studies. Cochrane led the way in making protocols available to readers of the Cochrane Library. They ensure transparency in how reviews are prepared and allow the planned methods to be critiqued. Specification of the review question (through setting the review's objectives) and the criteria for including studies are critical to the success of the review and the first two sections of the Standards address these tasks. The following section addresses selection of the outcomes of interest, an important aspect that should be prespecified carefully to avoid the need for post hoc decisions that could be influenced by the data.

The remaining Standards address the detailed methodology that will be followed during the review, covering the search for studies, selection of studies into the review, data collection, risk of bias assessment, synthesis (including any meta-analysis approaches), and overall assessment of the evidence. With few exceptions (such as use of the Cochrane Risk of Bias 2 tool for randomized trials), the precise methods to be used are not prescribed, For example, authors are free to use any meta-analysis method, although there is a potential convenience to both authors and readers if those implemented in Review Manager (RevMan) software are used.

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Developing the protocol of the review (C1-C23)

Cochrane Interactive Learning (CIL): Module 2-writing a protocol

Setting the research question to inform the scope of the review (C1-C4)

Setting the research question(s) to inform the scope of the review

Cochrane Training resource: defining the review question

Cochrane Interactive Learning (CIL): module 1 - introduction to conducting systematic reviews

	Standard	Rationale and elaboration	Resources
C1	*Formulating review questions*	***Mandatory***	
	Ensure that the review question and particularly the outcomes of interest, address issues that are important to review users such as consumers, health professionals and policy makers.	Cochrane Reviews are intended to support clinical practice and policy, not just scientific curiosity. The needs of consumers play a central role in Cochrane Reviews and they can play an important role in defining the review question.	See *Handbook* Section 2.1

		Qualitative research, i.e. studies that explore the experience of those involved in providing and receiving interventions, and studies evaluating factors that shape the implementation of interventions, might be used in the same way.	
C2	*Predefining objectives*	***Mandatory***	
	Define in advance the objectives of the review, including participants, interventions, comparators and outcomes (PICO).	Objectives give the review focus and must be clear before appropriate eligibility criteria can be developed. If the review will address multiple interventions, clarity is required on how these will be addressed (e.g. summarized separately, combined or explicitly compared).	See *Handbook* Section 2.3
C3	*Considering potential adverse effects*	***Mandatory***	
	Consider any important potential adverse effects of the intervention(s) and ensure that they are addressed.	It is important that adverse effects are addressed in order to avoid one-sided summaries of the evidence. At a minimum, the review will need to highlight the extent to which potential adverse effects have been evaluated in any included studies. Sometimes data on adverse effects are best obtained from non-randomized studies, or qualitative research studies. This does not mean however that all reviews must include non-randomized studies.	See *Handbook* Section 2.1 Cochrane Training resource: adverse effects
C4	*Considering equity and specific populations*	***Highly desirable***	
	Consider in advance whether issues of equity and relevance of evidence to specific populations are important to the review, and plan for appropriate methods to address them if they are. Attention should be paid to the relevance of the review question to populations such as low-socioeconomic groups, low- or middle-income regions, women, children and older people.	Where possible reviews should include explicit descriptions of the effect of the interventions not only upon the whole population, but also on the disadvantaged, and/or the ability of the interventions to reduce socioeconomic inequalities in health, and to promote use of the interventions to the community.	See *Handbook* Section 2.4 Cochrane Training resources: equity issues and PRISMA-E 2012

Setting eligibility criteria for including studies in the review (C5-C13)

Setting the eligibility criteria for including studies in the review

Cochrane Training resource: defining the review question

Cochrane Interactive Learning (CIL): module 2 - writing the review protocol

	Standard	Rationale and elaboration	Resources
C5	*Predefining unambiguous criteria for participants*	***Mandatory***	
	Define in advance the eligibility criteria for participants in the studies.	Predefined, unambiguous eligibility criteria are a fundamental prerequisite for a systematic review. The criteria for considering types of people included in studies in a review should be sufficiently broad to encompass the likely diversity of studies, but sufficiently narrow to ensure that a meaningful answer can be obtained when studies are considered in aggregate. Considerations when specifying participants include setting, diagnosis or definition of condition and demographic factors. Any restrictions to study populations must be based on a sound rationale, since it is important that Cochrane Reviews are widely relevant.	See *Handbook* Section 3.2.1
C6	*Predefining a strategy for studies with a subset of eligible participants*	***Highly desirable***	
	Define in advance how studies that include only a subset of relevant participants will be addressed.	Sometimes a study includes some 'eligible' participants and some 'ineligible' participants, for example when an age cut-off is used in the review's eligibility criteria. If data from the eligible participants cannot be retrieved, a mechanism for dealing with this situation should be prespecified.	See *Handbook* Section 3.2.1
C7	*Predefining unambiguous criteria for interventions and comparators*	***Mandatory***	
	Define in advance the eligible interventions and the interventions against which these can be compared in the included studies.	Predefined, unambiguous eligibility criteria are a fundamental prerequisite for a systematic review. Specification of comparator interventions requires particular clarity: are the experimental interventions to be compared with an inactive control intervention (e.g. placebo, no treatment, standard care, or a	See *Handbook* Section 3.2.2

		waiting list control), or with an active control intervention (e.g. a different variant of the same intervention, a different drug, a different kind of therapy)? Any restrictions on interventions and comparators, for example, regarding delivery, dose, duration, intensity, cointerventions and features of complex interventions should also be predefined and explained.	
C8	*Clarifying role of outcomes*	***Mandatory***	
	Clarify in advance whether outcomes listed under 'Criteria for considering studies for this review' are used as criteria for including studies (rather than as a list of the outcomes of interest within whichever studies are included).	Outcome measures should not always form part of the criteria for including studies in a review. However, some reviews do legitimately restrict eligibility to specific outcomes. For example, the same intervention may be studied in the same population for different purposes (e.g. hormone replacement therapy, or aspirin); or a review may address specifically the adverse effects of an intervention used for several conditions. If authors do exclude studies on the basis of outcomes, care should be taken to ascertain that relevant outcomes are not available because they have not been measured rather than simply not reported.	See *Handbook* Section 3.2.4.1
C9	*Predefining study designs*	***Mandatory***	
	Define in advance the eligibility criteria for study designs in a clear and unambiguous way, with a focus on features of a study's design rather than design labels.	Predefined, unambiguous eligibility criteria are a fundamental prerequisite for a systematic review. This is particularly important when non-randomized studies are considered. Some labels commonly used to define study designs can be ambiguous. For example a ‘double blind’ study may not make it clear who was blinded; a ‘case control’ study may be nested within a cohort, or be undertaken in a cross-sectional manner; or a ‘prospective’ study may have only some features defined or undertaken prospectively.	See *Handbook* Section 3.3
C10	*Including randomized trials*	***Mandatory***	
	Include randomized trials as	Randomized trials are the best	See *Handbook* Section 3.3.1

	eligible for inclusion in the review, *if it is feasible to conduct them to evaluate interventions and outcomes of interest.*	study design for evaluating the efficacy of interventions. If it is feasible to conduct them to evaluate questions that are being addressed by the review, they must be considered eligible for the review. However, appropriate exclusion criteria may be put in place, for example regarding length of follow-up.	
C11	*Justifying choice of study designs*	***Mandatory***	
	Justify the choice of eligible study designs.	It might be difficult to address some interventions or some outcomes in randomized trials. Authors should be able to justify why they have chosen either to restrict the review to randomized trials or to include non-randomized studies. The particular study designs included should be justified with regard to appropriateness to the review question and with regard to potential for bias.	See *Handbook* Section 3.3
C12	*Excluding studies based on publication status*	***Mandatory***	
	Include studies irrespective of their publication status, unless exclusion is explicitly justified.	Obtaining and including data from unpublished studies (including grey literature) can reduce the effects of publication bias. However, the unpublished studies that can be located may be an unrepresentative sample of all unpublished studies.	See *Handbook* Section 3.4
C13	*Changing eligibility criteria*	***Mandatory***	
	Justify any changes to eligibility criteria or outcomes studied. In particular, post hoc decisions about inclusion or exclusion of studies should keep faith with the objectives of the review rather than with arbitrary rules.	Following prespecified eligibility criteria is a fundamental attribute of a systematic review. However, unanticipated issues may arise. Review authors should make sensible post hoc decisions about exclusion of studies, and these should be documented in the review, possibly accompanied by sensitivity analyses. Changes to the protocol must not be made on the basis of the findings of the studies or the synthesis, as this can introduce bias.	See *Handbook* *Section 3.2.1*

Selecting outcomes to be addressed for studies included in the review (C14-C18)

Selecting outcomes to be addressed for studies included in the review

Cochrane Training resource: defining the review question

Cochrane Interactive Learning: module 2 - writing the review protocol

	Standard	Rationale and elaboration	Resources
C14	*Predefining outcome domains*	***Mandatory***	
	Define in advance outcomes that are critical to the review, and any additional important outcomes.	Full specification of the outcomes includes consideration of outcome domains (e.g. quality of life) and outcome measures (e.g. SF-36). Predefinition of outcome reduces the risk of selective outcome reporting. The *critical outcomes* should be as few as possible and should normally reflect at least one potential benefit and at least one potential area of harm. It is expected that the review should be able to synthesize these outcomes if eligible studies are identified, and that the conclusions of the review will be based largely on the effects of the interventions on these outcomes. Additional important outcomes may also be specified. Up to seven critical and important outcomes will form the basis of the GRADE assessment and summarized in the review's abstract and other summary formats, although the review may measure more than seven outcomes.	See *Handbook* *Section 3.2.4.1* Planning GRADE and Summary of Findings tables
C15	*Choosing outcomes*	***Mandatory***	
	Choose only outcomes that are critical or important to users of the review such as healthcare consumers, health professionals and policy makers.	Cochrane Reviews are intended to support clinical practice and policy, and should address outcomes that are critical or important to consumers. These should be specified at protocol stage. Where available, established sets of core outcomes should be used. Patient-reported outcomes should be included where possible. It is also important to judge whether evidence of resource use and costs might be an important component of decisions to adopt the intervention or alternative management strategies around the world. Large numbers of outcomes, while sometimes necessary, can make reviews unfocussed,	See *Handbook* Section 3.2.4.1

		unmanageable for the user, and prone to selective outcome reporting bias. Biochemical, interim and process outcomes should be considered where they are important to decision makers. Any outcomes that would not be described as critical or important can be left out of the review.	
C16	*Predefining outcome measures*	***Highly desirable***	
	Define in advance details of what will constitute acceptable outcome measures (e.g. diagnostic criteria, scales, composite outcomes).	Having decided what outcomes are of interest to the review, authors should clarify acceptable ways in which these outcomes can be measured. It may be difficult, however, to predefine adverse effects.	See *Handbook* Section 3.2.4.1
C17	*Predefining choices from multiple outcome measures*	***Highly desirable***	
	Define in advance how outcome measures will be selected when there are several possible measures (e.g. multiple definitions, assessors or scales).	Prespecification guards against selective outcome reporting, and allows users to confirm that choices were not overly influenced by the results. A predefined hierarchy of outcomes measures may be helpful. It may be difficult, however, to predefine adverse effects. A rationale should be provided for the choice of outcome measure.	See *Handbook* Section 3.2.4.1
C18	*Predefining time points of interest*	***Highly desirable***	
	Define in advance the timing of outcome measurement.	Prespecification guards against selective outcome reporting, and allows users to confirm that choices were not overly influenced by the results. Authors may consider whether all time frames or only selected time points will be included in the review. These decisions should be based on outcomes important for making healthcare decisions. One strategy to make use of the available data could be to group time points into prespecified intervals to represent 'short-term', 'medium-term' and 'long-term' outcomes and to take no more than one from each interval from each study for any particular outcome.	See *Handbook* Section 3.2.4.1

Planning the review methods at protocol stage (C19-C23)

Planning the review methods at protocol stage

	Standard	Rationale and elaboration	Resources
C19	*Planning the search*	***Mandatory***	
	Plan in advance the methods to be used for identifying studies. Design searches to capture as many studies as possible that meet the eligibility criteria, ensuring that relevant time periods and sources are covered and not restricted by language or publication status.	Searches should be motivated directly by the eligibility criteria for the review, and it is important that all types of eligible studies are considered when planning the search. If searches are restricted by publication status or by language of publication, there is a possibility of publication bias, or language bias (whereby the language of publication is selected in a way that depends on the findings of the study), or both. Removing language restrictions in English language databases is not a good substitute for searching non-English language journals and databases.	See *Handbook* Section 1.5; 4.3.1.1 Cochrane Training resource: searching studies CIL: module 3 - searching for studies
C20	*Planning the assessment of risk of bias in included studies*	***Mandatory***	
	Plan in advance the methods to be used for assessing risk of bias in included studies, including the tool(s) to be used, how the tool(s) will be implemented, and the criteria used to assign studies, for example, to judgements of low risk, high risk and unclear risk of bias.	Predefining the methods and criteria for assessing risk of bias is important since analysis or interpretation of the review findings may be affected by the judgements made during this process. For randomized trials, use of the Cochrane 'risk of bias' tool is Mandatory, so it is sufficient (and easiest) simply to refer to the definitions of low risk, unclear risk and high risk of bias provided in the *Handbook*.	See *Handbook* Section 1.5 Cochrane Training resource: risk of bias
C21	*Planning the synthesis of results*	***Mandatory***	
	Plan in advance the methods to be used to synthesize the results of the included studies, including whether a quantitative synthesis is planned, how heterogeneity will be assessed, choice of effect measure (e.g. odds ratio, risk ratio, risk difference or other for dichotomous outcomes), and methods for meta-analysis (e.g. inverse variance or Mantel Haenszel, fixed-effect or random-effects model).	Predefining the synthesis methods, particularly the statistical methods, is important, since analysis or interpretation of the review findings may be affected by the judgements made during this process.	See *Handbook* Section 1.5 Cochrane Training resources: meta-analysis; dichotomous outcomes; continuous outcomes and heterogeneity CIL: module 6 - analysing the data
C22	*Planning sub-group analyses*	***Mandatory***	

	Predefine potential effect modifiers (e.g. for subgroup analyses) at the protocol stage; restrict these in number, and provide rationale for each.	Prespecification reduces the risk that large numbers of undirected subgroup analyses will lead to spurious explanations of heterogeneity.	See *Handbook* Section 1.5 Cochrane Training resource: heterogeneity CIL: module 6 - analysing the data
C23	*Planning the GRADE assessment and 'Summary of findings' table*	***Mandatory***	
	Plan in advance the methods to be used for assessing the quality of the body of evidence, and summarizing the findings of the review.	Methods for assessing the quality of evidence for the most important outcomes in the review need to be prespecified. In 'Summary of findings' tables the most important feature is to predefine the choice of outcomes in order to guard against selective presentation of results in the review. The table should include the essential outcomes for decision making (typically up to seven), which generally should not include surrogate or interim outcomes. The choice of outcomes should not be based on any anticipated or observed magnitude of effect, or because they are likely to have been addressed in the studies to be reviewed.	See *Handbook* Section 1.5 Cochrane Training resource: evaluating evidence CIL: module 7 - interpreting the findings Planning GRADE and Summary of Findings tables

Performing the review (C24-C75)

Searching for studies (C24-C38)

Searching for studies

Cochrane Training resource: searching for studies

Cochrane Interactive Learning (CIL): module 3 - searching for studies

	Standard	**Rationale and elaboration**	**Resources**
C24	*Searching general bibliographic databases and CENTRAL*	***Mandatory***	
	Search the Cochrane Review Group's (CRG's) Specialized Register (internally, e.g. via the Cochrane Register of Studies, or externally via CENTRAL). Ensure that CENTRAL, MEDLINE (e.g. via PubMed) and Embase (if Embase is	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible. The minimum databases to be covered are the CRG's Specialized Register	See *Handbook* Section 4.3.1.1 Cochrane Training resource: Register of Studies and RevMan

	available to either the CRG or the review author), have been searched (either for the review or for the Review Group's Specialized Register).	(if it exists and was designed to support reviews in this way), CENTRAL, MEDLINE and Embase (if Embase is available to either the CRG or the review author). Expertise may be required to avoid unnecessary duplication of effort. Some, but not all, reports of eligible studies from MEDLINE, Embase and the CRGs' Specialized Registers are already included in CENTRAL.	
C25	*Searching specialist bibliographic databases*	***Highly desirable***	
	Search appropriate national, regional and subject-specific bibliographic databases.	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible. Databases relevant to the review topic should be covered (e.g. CINAHL for nursing-related topics, APA PsycInfo for psychological interventions), and regional databases (e.g. LILACS) should be considered.	See *Handbook* Section 4.3.1.4
C26	*Searching for different types of evidence*	***Mandatory***	
	If the review has specific eligibility criteria around study design to address adverse effects, economic issues or qualitative research questions, undertake searches to address them.	Sometimes a review will address questions about adverse effects, economic issues or qualitative research using a different set of eligibility criteria from the main (effectiveness) component. In such situations, the searches for evidence must be suitable to identify relevant study designs for these questions. Different searches may need to be conducted for different types of evidence.	See *Handbook* Section 4.4.1 Cochrane Training resource: searching for adverse effects
C27	*Searching trials registers*	***Mandatory***	
	Search trials registers and repositories of results, where relevant to the topic, through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) portal and other sources as appropriate.	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible. Although ClinicalTrials.gov is included as one of the registers within the WHO ICTRP portal, it is recommended that both ClinicalTrials.gov and the ICTRP portal are searched separately due to additional features in ClinicalTrials.gov.	See *Handbook* Section 4.3.3

C28	*Searching for grey literature*	***Highly desirable***	
	Search relevant grey literature sources such as reports, dissertations, theses and conference abstracts.	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible.	See *Handbook* Section 4.3.5
C29	*Searching within other reviews*	***Highly desirable***	
	Search within previous reviews on the same topic.	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible.	See *Handbook* Section 4.3.5
C30	*Searching reference lists*	***Mandatory***	
	Check reference lists in included studies and any relevant systematic reviews identified.	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible.	See *Handbook* Section 4.3.5
C31	*Searching by contacting relevant individuals and organizations*	***Highly desirable***	
	Contact relevant individuals and organizations for information about unpublished or ongoing studies.	Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible. It is important to identify ongoing studies, so that these can be assessed for possible inclusion when a review is updated.	See *Handbook* Section 4.3.2
C32	*Structuring search strategies for bibliographic databases*	***Mandatory***	
	Inform the structure of search strategies in bibliographic databases around the main concepts of the review, using appropriate elements from PICO and study design. In structuring the search, maximize sensitivity whilst striving for reasonable precision. Ensure correct use of the 'AND' and 'OR' operators.	Inappropriate or inadequate search strategies may fail to identify records that are included in bibliographic databases. Expertise may need to be sought, in particular from the CRG's Information Specialist. The structure of a search strategy should be based on the main concepts being examined in a review. In general databases, such as MEDLINE, a search strategy to identify studies for a Cochrane Review will typically have three sets of terms: 1) terms to search for the health condition of interest, i.e. the population; 2) terms to search for the intervention(s) evaluated; and 3) terms to search for the types of study design to be included	See *Handbook* Section 4.4.2

		(typically a 'filter' for randomized trials). There are exceptions, however. For instance, for reviews of complex interventions, it may be necessary to search only for the population or the intervention. Within each concept, terms are joined together with the Boolean 'OR' operator, and the concepts are combined with the Boolean 'AND' operator. The 'NOT' operator should be avoided where possible to avoid the danger of inadvertently removing records that are relevant from the search set.	
C33	*Developing search strategies for bibliographic databases*	***Mandatory***	
	Identify appropriate controlled vocabulary (e.g. MeSH, Emtree, including 'exploded' terms) and free-text terms (considering, for example, spelling variants, synonyms, acronyms, truncation and proximity operators).	Inappropriate or inadequate search strategies may fail to identify records that are included in bibliographic databases. Search strategies need to be customized for each database. It is important that MeSH terms are 'exploded' wherever appropriate, in order not to miss relevant articles. The same principle applies to Emtree when searching Embase and also to a number of other databases. The controlled vocabulary search terms for MEDLINE and Embase are not identical, and neither is the approach to indexing. In order to be as comprehensive as possible, it is necessary to include a wide range of free-text terms for each of the concepts selected. This might include the use of truncation and wildcards. Developing a search strategy is an iterative process in which the terms that are used are modified, based on what has already been retrieved.	See *Handbook* Section 4.4.4
C34	*Using search filters*	***Highly desirable***	
	Use specially designed and tested search filters where appropriate including the Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE, but do not use filters in pre-filtered databases e.g. do not use a randomized trial filter	Inappropriate or inadequate search strategies may fail to identify records that are included in bibliographic databases. Search filters should be used with caution. They should be assessed not only for the reliability of their development and reported	See *Handbook* Section 4.4.7

	in CENTRAL.	performance, but also for their current accuracy, relevance and effectiveness given the frequent interface and indexing changes affecting databases.	
C35	*Restricting database searches*	***Mandatory***	
	Justify the use of any restrictions in the search strategy on publication date and publication format.	Date restrictions in the search should only be used when there are date restrictions in the eligibility criteria for studies. They should be applied only if it is known that relevant studies could only have been reported during a specific time period, for example if the intervention was only available after a certain time point. Searches for updates to reviews might naturally be restricted by date of entry into the database (rather than date of publication) to avoid duplication of effort. Publication format restrictions (e.g. exclusion of letters) should generally not be used in Cochrane Reviews, since any information about an eligible study may be of value.	See *Handbook* Section 4.4.5
C36	*Documenting the search process*	***Mandatory***	
	Document the search process in enough detail to ensure that it can be reported correctly in the review.	The search process (including the sources searched, when, by whom, and using which terms) needs to be documented in enough detail throughout the process to ensure that it can be reported correctly in the review, to the extent that all the searches of all the databases are reproducible.	See *Handbook* Section 4.4.5
C37	*Rerunning searches*	***Mandatory***	
	Rerun or update searches for all relevant sources within 12 months before publication of the review or review update, and screen the results for potentially eligible studies.	The published review should be as up to date as possible. The search must be rerun close to publication, if the initial search date is more than 12 months (preferably six months) from the intended publication date, and the results screened for potentially eligible studies. Ideally the studies should be incorporated fully in the review. If not, then the potentially eligible studies will need to be reported, at a minimum as a reference under ‘Studies awaiting classification’ (or ‘Ongoing studies’ if they have not yet completed).	See *Handbook* Section 4.4.10

C38	*Incorporating findings from rerun searches*	***Highly desirable***	
	Fully incorporate any studies identified in the rerun or update of the search within 12 months before publication of the review or review update.	The published review should be as up to date as possible. After the rerun of the search, the decision whether to incorporate any new studies fully into the review will need to be balanced against the delay in publication.	See *Handbook* Section 4.4.10

Selecting studies to include in the review (C39-C42)

Selecting studies to include in the review

Cochrane Training resources: selecting studies and Covidence webinar (online tool for review production)

Cochrane Interactive Learning (CIL): module 4 - selecting studies and collecting data

	Standard	**Rationale and elaboration**	**Resources**
C39	*Making inclusion decisions*	***Mandatory***	
	Use (at least) two people working independently to determine whether each study meets the eligibility criteria, and define in advance the process for resolving disagreements.	Duplicating the study selection process reduces both the risk of making mistakes and the possibility that selection is influenced by a single person's biases. The inclusion decisions should be based on the full texts of potentially eligible studies when possible, usually after an initial screen of titles and abstracts. It is desirable, but not mandatory, that two people undertake this initial screening, working independently.	See *Handbook* Section 4.6.4
C40	*Excluding studies without useable data*	***Mandatory***	
	Include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.	Systematic reviews typically should seek to include all relevant participants who have been included in eligible study designs of the relevant interventions and had the outcomes of interest measured. Reviews must not exclude studies solely on the basis of *reporting* of the outcome data, since this may introduce bias due to selective outcome reporting and risk undermining the systematic review process. While such studies cannot be included in meta-analyses, the implications of their omission should be considered. Note that studies may legitimately be	See *Handbook* Section 4.6.3

		excluded because outcomes were not *measured*. Furthermore, issues may be different for adverse effects outcomes, since the pool of studies may be much larger and it can be difficult to assess whether such outcomes were measured.	
C41	*Documenting decisions about records identified*	***Mandatory***	
	Document the selection process in sufficient detail to be able to complete a flow diagram and a table of 'Characteristics of excluded studies'.	Decisions should therefore be documented for all records identified by the search. Numbers of records are sufficient for exclusions based on initial screening of titles and abstracts. Broad categorizations are sufficient for records classed as potentially eligible during an initial screen. Studies listed in the table of 'Characteristics of excluded studies' should be those that a user might reasonably expect to find in the review. At least one explicit reason for their exclusion must be documented. Authors will need to decide for each review when to map records to studies (if multiple records refer to one study). Lists of included and excluded studies must be based on studies rather than records.	See *Handbook* Section 4.6.4
C42	*Collating multiple reports*	***Mandatory***	
	Collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review.	It is wrong to consider multiple reports of the same study as if they are multiple studies. Secondary reports of a study should not be discarded, however, since they may contain valuable information about the design and conduct. Review authors must choose and justify which report to use as a source for study results.	See *Handbook* Sections 4.6.2; 5.2.1

Collecting data from included studies (C43-C51)

Collecting data from included studies

Cochrane Training resources: collecting data and Covidence webinar (online tool for review production)

Cochrane Interactive Learning (CIL): module 4 - selecting studies and collecting data

	Standard	Rationale and elaboration	Resources
C43	*Using data collection forms*	***Mandatory***	

	Use a data collection form which has been piloted.	Review authors often have different backgrounds and level of systematic review experience. Using a data collection form ensures some consistency in the process of data extraction, and is necessary for comparing data extracted in duplicate. The completed data collection forms should be available to the CRG on request. Piloting the form within the review team is highly desirable. At a minimum, the data collection form (or a very close variant of it) must have been assessed for usability.	See *Handbook* Section 5.4.1
C44	*Describing studies*	***Mandatory***	
	Collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies'.	Basic characteristics of each study will need to be presented as part of the review, including details of participants, interventions and comparators, outcomes and study design.	See *Handbook* Section 5.3.1
C45	*Extracting study characteristics in duplicate*	***Highly desirable***	
	Use (at least) two people working independently to extract study characteristics from reports of each study, and define in advance the process for resolving disagreements.	Duplicating the data extraction process reduces both the risk of making mistakes and the possibility that data selection is influenced by a single person's biases. Dual data extraction may be less important for study characteristics than it is for outcome data, so it is not a mandatory standard for the former.	See *Handbook* Section 5.5.2
C46	*Extracting outcome data in duplicate*	***Mandatory***	
	Use (at least) two people working independently to extract outcome data from reports of each study, and define in advance the process for resolving disagreements.	Duplicating the data extraction process reduces both the risk of making mistakes and the possibility that data selection is influenced by a single person's biases. Dual data extraction is particularly important for outcome data, which feed directly into syntheses of the evidence, and hence to the conclusions of the review.	See *Handbook* Section 5.5.2
C47	*Making maximal use of data*	***Mandatory***	
	Collect and utilize the most detailed numerical data that might facilitate similar analyses of included studies. Where 2×2 tables or means and standard deviations are not available, this might include effect estimates (e.g. odds ratios,	Data entry into RevMan is easiest when 2×2 tables are reported for dichotomous outcomes, and when means and standard deviations are presented for continuous outcomes. Sometimes these statistics are not reported but	See *Handbook* Section 5.3.6 Cochrane Training resources: dichotomous outcomes and continuous outcomes

	regression coefficients), confidence intervals, test statistics (e.g. t, F, Z, Chi^2) or P values, or even data for individual participants.	some manipulations of the reported data can be performed to obtain them. For instance, 2×2 tables can often be derived from sample sizes and percentages, while standard deviations can often be computed using confidence intervals or P values. Furthermore, the inverse-variance data entry format can be used even if the detailed data required for dichotomous or continuous data are not available, for instance if only odds ratios and their confidence intervals are presented. The RevMan calculator facilitates many of these manipulations.	
C48	*Examining errata*	***Mandatory****	
	Examine any relevant retraction statements and errata for information.	Some studies may have been found to be fraudulent or articles about them may have been retracted since publication for other reasons. Errata can reveal important limitations, or even fatal flaws, in included studies. All of these may lead to the potential exclusion of a study from a review or meta-analysis. Care should be taken to ensure that this information is retrieved in all database searches by downloading the appropriate fields, together with the citation data.	See *Handbook* Section 4.4.5
C49	*Obtaining unpublished data*	***Highly desirable***	
	Seek key unpublished information that is missing from reports of included studies.	Contacting study authors to obtain or confirm data makes the review more complete, potentially enhances precision and reduces the impact of reporting biases. Missing information includes details to inform 'risk of bias' assessments, details of interventions and outcomes, and study results (including breakdowns of results by important subgroups).	See *Handbook* Section 5.2.3
C50	*Choosing interventions in multi-arm studies*	***Mandatory***	
	If a study is included with more than two intervention arms,	There is no point including irrelevant interventions in the	See *Handbook* Section 5.3.6

	include in the review only the interventions that meet the eligibility criteria.	review. Authors, however, should make it clear in the 'Table of characteristics of included studies' that these interventions were present in the study.	Cochrane Training resource: non-standard data and study design
C51	*Checking accuracy of numeric data in the review*	***Mandatory***	
	Compare magnitude and direction of effects reported by studies with how they are presented in the review, taking account of legitimate differences.	This is a reasonably straightforward way for authors to check a number of potential problems, including typographical errors in studies' reports, accuracy of data collection and manipulation, and data entry into RevMan. For example, the direction of a standardized mean difference may accidentally be wrong in the review. A basic check is to ensure the same qualitative findings (e.g. direction of effect and statistical significance) between the data as presented in the review and the data as available from the original study. Results in forest plots should agree with data in the original report (point estimate and confidence interval) if the same effect measure and statistical model is used.	See *Handbook* Section 5.3.6

Assessing risk of bias in included studies (C52-C60)

Cochrane Training resources: assessing RoB and RoB 2.0 webinar

Cochrane Interactive Learning (CIL): module 5 - introduction to study quality and risk of bias

	Standard	**Rationale and elaboration**	**Resources**
C52	*Assessing risk of bias*	***Mandatory***	
	Assess the risk of bias for each study result contributing to an outcome in the 'summary of findings' table. For randomized trials, the RoB 2 tool should be used, involving judgements and support for those judgements across a series of domains of bias, as described in the *Handbook.*	Risk of bias in individual study results for the included studies should be explicitly considered to determine the extent to which findings of the studies can be believed. Risks of bias might vary by result. It may not be feasible to assess the risk of bias in every single result available across the included studies, particularly if a large number of studies and results are available. Review author should therefore assess risk of bias in the results of outcomes included in their 'summary of findings' tables, which present	See *Handbook* Section 7.1.2; Chapter 8

		the findings of seven or fewer outcomes that are most important to patients. The RoB 2 tool – as described in the *Handbook*– is the preferred tool for all randomized trials in new reviews. The Cochrane Evidence Production and Methods Directorate is, however, aware that there remain challenges in learning and implementation of the tool, and use of the original Cochrane risk of bias tool is acceptable for the time being.	
C53	*Assessing risk of bias in duplicate*	***Mandatory***	
	Use (at least) two people working independently to apply the risk-of-bias tool to each included study, and define in advance the process for resolving disagreements.	Duplicating the risk-of-bias assessment reduces both the risk of making mistakes and the possibility that assessments are influenced by a single person's biases.	See *Handbook* Section 7.3.2; Chapter 8
C54	*Supporting judgements of risk of bias*	***Mandatory***	
	Justify judgements of risk of bias (high, low and some concerns) and provide this information in the risk-of-bias tables (as 'Support for judgement').	Providing support for the judgement makes the process transparent.	See *Handbook* Section 7.3.2; Chapter 8
C55	*Providing sources of information for risk of bias assessments*	***Mandatory***	
	Collect the source of information for each risk of bias judgement (e.g. quotation, summary of information from a trial report, correspondence with investigator etc.). Where judgements are based on assumptions made on the basis of information provided outside publicly available documents, this should be stated.	Readers, editors and referees should have the opportunity to see for themselves from where supports for judgements have been obtained.	See *Handbook* Section 7.3.2; Chapter 8
C56	*Summarizing risk-of-bias assessments.*	***Highly desirable***	
	Summarize the risk of bias for each key outcome for each study	This reinforces the link between the characteristics of the study design and their possible impact on the results of the study and is an important prerequisite for the GRADE approach to assessing the certainty of the body of evidence.	See *Handbook* Section 7.5; Chapter 8
C57	*Addressing risk of bias in the*	***Highly desirable***	

	synthesis.		
	Address risk of bias in the synthesis (whether quantitative or non-quantitative). For example, present analyses stratified according to summary risk of bias, or restricted to studies at low risk of bias.	Review authors should consider how study biases affect results. This is useful in determining the strength of conclusions and how future research should be designed and conducted.	See *Handbook* Section 7.6.1; Chapter 8
C58	*Incorporating assessments of risk of bias.*	***Mandatory***	
	If randomized trials have been assessed using one or more tools in addition to the RoB 2 tool, use the RoB 2 tool as the primary assessment of bias for interpreting results, choosing the primary analysis, and drawing conclusions.	For consistency of approach across Cochrane Intervention Reviews, the RoB 2 tool should take precedence when two or more tools are used for assessing risk of bias in randomized trials. The RoB 2 tool also feeds directly into the GRADE approach for assessing the certainty of the body of evidence.	See *Handbook* Section 7.6.1; Chapter 8
C59	*Addressing conflicts of interest in included trials.*	***Highly desirable***	
	Address conflict of interests in included trials, and reflect on possible impact on: a) differences in study design; b) risk of bias in trial result, and c) risk of bias in synthesis result	Review authors should consider assessing whether they judge a trial to be of "notable concern about conflicts of interest". This assessment is useful for exploration of possible heterogeneity between trials (e.g. in a subgroup analysis), and for reflection on relevant mechanisms for how conflict of interest may have biased trial results and synthesis results. Concerns about conflicts of interest can be reported in the 'Characteristics of included studies' table.	See *Handbook* Section 7.8.6; Chapter 8
C60	*Not applicable*		

Synthesizing the results of included studies (C61-C73)

Synthesizing the results of included studies

Cochrane Interactive Learning (CIL): module 6 - analysing the data

	Standard	**Rationale and elaboration**	**Resources**
C61	*Combining different scales*	***Mandatory***	
	If studies are combined with different scales, ensure that	Sometimes scales have higher scores that reflect a 'better'	See *Handbook* Section 6.5.1

	higher scores for continuous outcomes all have the same meaning for any particular outcome; explain the direction of interpretation; and report when directions are reversed.	outcome and sometimes lower scores reflect 'better' outcome. Meaningless (and misleading) results arise when effect estimates with opposite clinical meanings are combined.	
C62	*Ensuring meta-analyses are meaningful*	***Mandatory***	
	Undertake (or display) a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful.	Meta-analyses of very diverse studies can be misleading, for example where studies use different forms of control. Clinical diversity does not indicate necessarily that a meta-analysis should not be performed. However, authors must be clear about the underlying question that all studies are addressing.	See *Handbook* Section 10.10.1
C63	*Assessing statistical heterogeneity*	***Mandatory***	
	Assess the presence and extent of between-study variation when undertaking a meta-analysis.	The presence of heterogeneity affects the extent to which generalizable conclusions can be formed. It is important to identify heterogeneity in case there is sufficient information to explain it and offer new insights. Authors should recognize that there is much uncertainty in measures such as I^2 and Tau^2 when there are few studies. Thus, use of simple thresholds to diagnose heterogeneity should be avoided.	See *Handbook* Section 10.10.2 Cochrane Training resource: exploring heterogeneity
C64	*Addressing missing outcome data*	***Highly desirable***	
	Consider the implications of missing outcome data from individual participants (due to losses to follow-up or exclusions from analysis).	Incomplete outcome data can introduce bias. In most circumstances, authors should follow the principles of intention-to-treat analyses as far as possible (this may not be appropriate for adverse effects or if trying to demonstrate equivalence). Risk of bias due to incomplete outcome data is addressed in the Cochrane 'risk- of-bias' tool. However, statistical analyses and careful interpretation of results are additional ways in which the issue can be addressed by review authors. Imputation methods can be considered (accompanied by, or in the form of, sensitivity analyses).	See *Handbook* Section 10.12.1 Cochrane Training resources: assessing RoB included studies and RoB 2.0 webinar
C65	*Addressing skewed data*	***Highly desirable***	
	Consider the possibility and	Skewed data are sometimes	See *Handbook* Section 10.5.3

	implications of skewed data when analysing continuous outcomes.	not summarized usefully by means and standard deviations. While statistical methods are approximately valid for large sample sizes, skewed outcome data can lead to misleading results when studies are small.	Cochrane Training resource: analysing continuous outcomes
C66	*Addressing studies with more than two groups*	***Mandatory***	
	If multi-arm studies are included, analyse multiple intervention groups in an appropriate way that avoids arbitrary omission of relevant groups and double-counting of participants.	Excluding relevant groups decreases precision and double counting increases precision spuriously; both are inappropriate and unnecessary. Alternative strategies include combining intervention groups, separating comparisons into different forest plots and using network meta-analysis.	See *Handbook* Section 6.2.9 and Chapter 11. Cochrane Training resource: analysing non-standard data & study designs
C67	*Comparing subgroups*	***Mandatory***	
	If subgroup analyses are to be compared, and there are judged to be sufficient studies to do this meaningfully, use a formal statistical test to compare them.	Concluding that there is a difference in effect in different subgroups on the basis of differences in the level of statistical significance within subgroups can be very misleading.	See *Handbook* Section 10.11.3.1 Cochrane Training resources: exploring heterogeneity and common interpretation errors
C68	*Interpreting subgroup analyses*	***Mandatory***	
	If subgroup analyses are conducted, follow the subgroup analysis plan specified in the protocol without undue emphasis on particular findings.	Selective reporting, or over-interpretation, of particular subgroups or particular subgroup analyses should be avoided. This is a problem especially when multiple subgroup analyses are performed. This does not preclude the use of sensible and honest post hoc subgroup analyses.	See *Handbook* Section 10.11.5.2 Cochrane Training resources: exploring heterogeneity and common interpretation errors
C69	*Considering statistical heterogeneity when interpreting the results*	***Mandatory***	
	Take into account any statistical heterogeneity when interpreting the results, particularly when there is variation in the direction of effect.	The presence of heterogeneity affects the extent to which generalizable conclusions can be formed. If a fixed-effect analysis is used, the confidence intervals ignore the extent of heterogeneity. If a random-effects analysis is used, the result pertains to the mean effect across studies. In both cases, the implications of notable heterogeneity should be addressed. It may be possible to understand the reasons for	See *Handbook* Section 10.10.3 Cochrane Training resource: exploring heterogeneity

		the heterogeneity if there are sufficient studies.	
C70	*Addressing non-standard designs*	***Mandatory***	
	Consider the impact on the analysis of clustering, matching or other non-standard design features of the included studies	Cluster-randomized trials, cross-over trials, studies involving measurements on multiple body parts, and other designs need to be addressed specifically, since a naive analysis might underestimate or overestimate the precision of the study. Failure to account for clustering is likely to overestimate the precision of the study,that is, to give it confidence intervals that are too narrow and a weight that is too large. Failure to account for correlation is likely to underestimate the precision of the study, that is, to give it confidence intervals that are too wide and a weight that is too small.	See *Handbook* Section 6.2.1 Cochrane Training resource: non-standard study designs
C71	*Sensitivity analysis*	***Highly desirable***	
	Use sensitivity analyses to assess the robustness of results, such as the impact of notable assumptions, imputed data, borderline decisions and studies at high risk of bias.	It is important to be aware when results are robust, since the strength of the conclusion may be strengthened or weakened.	See *Handbook* Section 10.14 Cochrane Training resource: exploring heterogeneity
C72	*Interpreting results*	***Mandatory***	
	Focus interpretation of results on estimates of effect and their confidence intervals, avoiding use of a distinction between “statistically significant” and “statistically non-significant".	Authors commonly mistake a lack of evidence of effect as evidence of a lack of effect.	See *Handbook* Section 15.3.1 Cochrane Training resource: common interpretation errors CIL: module 7 - interpreting the findings
C73	*Investigating risk of bias due to missing results*	***Highly desirable***	
	Consider the potential impact of non-reporting biases on the results of the review or the meta-analyses it contains.	There is overwhelming evidence of non-reporting biases of various types. These can be addressed at various points in the review. A thorough search, and attempts to obtain unpublished results, might minimize the risk. Analyses of the results of included studies, for example using funnel plots, can sometimes help determine the possible extent of the problem, as can attempts to identify study protocols, which should be a routine feature of Cochrane Reviews.	See *Handbook* Section 13.4 Cochrane Training resources: small study effects & reporting biases CIL: module 7 - interpreting the findings

Assessing the quality of evidence and summarizing the findings (C74-C75)

Assessing the quality of evidence and summarizing the findings

Cochrane Training resource: GRADE approach to evaluating evidence quality

Cochrane Interactive Learning: module 7 - interpreting the findings

	Standard	Rationale and elaboration	Resources
C74	*Assessing the certainty of the body of evidence*	***Mandatory***	
	Use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review.	GRADE is the most widely used approach for summarizing confidence in effects of interventions by outcome across studies. It is preferable to use the online GRADEpro tool, and to use it as described in the help system of the software. This should help to ensure that author teams are accessing the same information to inform their judgments. Ideally, two people working independently should assess the certainty of the body of evidence and reach a consensus view on any downgrading decisions. The five GRADE considerations should be addressed irrespective of whether the review includes a 'Summary of findings' table. It is helpful to draw on this information in the Discussion, in the Authors' conclusions and to convey the certainty in the evidence in the Abstract and Plain language summary.	See *Handbook* Section 14.2.1 Common issues in Summary of Findings tables. Planning GRADE and Summary of Findings tables. Incorporating GRADE in Cochrane Reviews.
C75	*Justifying assessments of the certainty of the body of evidence*	***Mandatory***	
	Justify and document all assessments of the certainty of the body of evidence (for example downgrading or upgrading if using GRADE).	The adoption of a structured approach ensures transparency in formulating an interpretation of the evidence, and the result is more informative to the user.	See *Handbook* Section 14.2.1

Reference

Reference

Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. (2014) Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687. doi: 10.1136/bmj.g1687

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