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. 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.	See *Handbook* Section 2.1
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	See *Handbook* Section 2.1 Cochrane Training resource: adverse effects

		studies. This does not mean however that all reviews must include non-randomized studies.	
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*	***Highly desirable***	

	participants		
	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 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.	See *Handbook* Section 3.2.2
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	See *Handbook* Section 3.2.4.1

		measured rather than simply not reported.	
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 eligible for inclusion in the review, *if it is feasible to conduct them to evaluate interventions and outcomes of interest.*	Randomized trials are the best 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.	See *Handbook* Section 3.3.1
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	See *Handbook* Section 3.4

		be an unrepresentative sample of all unpublished studies.	
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	See *Handbook* *Section 3.2.4.1* Planning GRADE and Summary of Findings tables

		abstract and other summary formats, although the review may measure more than seven outcomes.	
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, 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.	See *Handbook* Section 3.2.4.1
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,	Predefining the methods and criteria for assessing risk of bias is important since analysis or interpretation of the review	See *Handbook* Section 1.5 Cochrane Training resource: risk of bias

	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.	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*.	
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