Writing your Protocol for a Cochrane Review

Last updated: October 2019
Important updates: New Edition of the Cochrane Handbook; RevMan Web; Risk of bias-2

Training/Resources

- Good practice resources for new Cochrane authors
- Online training is available at Cochrane Interactive Learning for both new and experienced authors, and you can earn certificates for modules successfully completed. (Please send any certificates obtained to us for our records)
- Specific 'Protocol' training is available on Cochrane Interactive Learning (Module 2: Writing the review protocol), and there is a webinar on Common errors and best practice when writing a review protocol, which may be useful.
- There are frequently webinars and other learning events posted here and on Cochrane Learning Live aimed at anyone interested in learning skills or gaining knowledge and experience relating to Cochrane activities. The series is managed by Cochrane's Learning and Support Department. The webinars are open to anyone wanting to learn in the Cochrane environment.
- Specific training and learning resources to help you understand the GRADE approach is also available.

Things to do before writing the draft protocol

- Ask Janne Vendt, our Cochrane Information Specialist (janne.vendt@regionh.dk), for help designing and peer-reviewing your search strategy (she cannot run your searches (see notes on search section)).
- Make sure you are using the latest desktop version of RevMan 5.3.5 (http://tech.cochrane.org/revman/download) and/or that you have access to RevMan Web (link explaining how to gain access), Cochrane's new browser-based review production platform (more info here, and training available here, and knowledgebase here)
- Once you do this, make sure that your version of RevMan (5.3.5) is displaying the MECIR standards pane (see page 3 of the RevMan 5 userguide – open RevMan/click on help/choose userguide).
- Be aware ALL Cochrane authors must make sure they use the MECIR standards for conducting, reporting and updating Cochrane protocols and reviews.
    - There are specific MECIR standards for Cochrane protocols (we refer to these throughout this guidance)
- You should check your review against the MECIR standards (you do this in RevMan 5 (desktop) by placing your cursor at the end of the relevant section (for example abstract objectives – the instructions for that section will appear in the pane on the right), and in RevMan Web by viewing the Standards tab under the Context panel on the right side of the browser

- The Cochrane Handbook can be found here (the new edition was released October 2019). It too offers much help and guidance for writing your protocol and conducting your review. Sections of interest may include 'Chapter II: Planning a Cochrane Review', 'Chapter II.1.4 Cochrane protocols', 'Chapter III.2 Reporting of protocols of new Cochrane Reviews', 'Chapter 2: Determining the scope of the review and the questions it will address', 'Chapter 3: Defining the criteria for including studies and how they will be grouped for synthesis'
- Text must appear under each of the blue headings in your RevMan 5 file unless you are directed otherwise (see instructions below). The required protocol sections will also be indicated in RevMan Web.
- Remember the predefined headings (and Handbook) guide you to what each section should contain. The MECIR standards will outline what each section should contain.
- Make sure to properly reference and attribute all statements
- Remember a protocol sets out what you plan to study not what you have done, so it should be written in the future tense and active voice. So, for example: 'we will search the following databases....'
- We use *Oxford English Dictionary* spellings: so, randomized with a 'z' but anaesthesia, paediatric, analyse. This resource may be helpful if you are unsure, or you can consult us.
- Make sure to run validation and spell checks before submitting your first draft to editorial board screening.
- Be aware that once a month we hold an Editorial Board teleconference and screen all new protocols. We find it to be an extremely efficient way to get feedback from many content and statistical editors. A decision will be made during the teleconference as to whether the protocol can proceed immediately to peers with either no or only minor edits; needs a major revision by the authors; or whether it should not proceed in the editorial process. We hope this process will speed the entire editorial process up, spot potential problems in the reviews earlier and mean that protocols (and reviews) proceed to publication earlier and with fewer problems.

Writing the Protocol

Title and Authors

- See MECIR (PR1-PR2)

Background

- No text should appear directly under this heading, see MECIR PR3-PR4

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).
- *Make sure to reference all statements, and attribute any direct quotations*

- *References should appear in alphabetical order, separated by semi colons and in round brackets (parentheses). They should be properly linked in the text.*

Description of the intervention

- A description of the experimental intervention(s) should place it 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 might describe the theoretical reasoning 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 a general problem.

Objectives

- See MECIR (PR5-PR8)
- This should begin with a precise statement of the primary objective of the review, ideally in a single sentence. Where possible the style should be of the 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. It is not necessary to state specific hypotheses.
- Ensure that the review question and particularly the outcomes of interest (and timeframes if relevant) address issues that are important to stakeholders such as consumers, health professionals and policymakers.
- Define in advance the objectives of the review, including participants, interventions, comparators and outcomes.
- Consider any important potential adverse effects of the intervention(s) and ensure that they are addressed.

Methods

- No text should appear directly under this heading

Criteria for considering studies for this review

- See MECIR (PR9-PR16)
- No text should appear under this heading

Types of studies

- PR9 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. Pre-defined, unambiguous eligibility criteria are a fundamental pre-requisite 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 is blind; 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 5.5, 13.2.2
- Including Randomized Trials: randomized trials are the best study design for evaluating the efficacy of interventions. If they are feasible for evaluating 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 the length of follow-up.
- See Handbook Chapter 3, MECIR Box 3.3.a

Types of participants

- PR11: participants in the studies. 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 the condition and demographic factors. Any restrictions to study populations must be based on sound rationale since it is important that Cochrane reviews are widely relevant. See Handbook Chapter 3.2.1
- Define in advance how studies that include only a subset of relevant participants will be handled. 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. In case data from the eligible participants cannot be retrieved, a mechanism for dealing with this situation should be pre-specified. See Handbook Chapter 3.2.1, MECIR Box 3.2.a

Types of interventions

- PR12 Define in advance the eligible interventions and the interventions against which these can be compared in the included studies. Pre-defined, unambiguous eligibility criteria are a fundamental pre-requisite 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, such as regarding delivery, dose, duration, intensity, co-interventions and features of complex interventions should also be pre-defined and explained. See Handbook Chapter 3.2.2.

Types of outcome measures

- No text should appear under this heading in the protocol
- PR13-16 Define in advance which outcomes are primary outcomes and which are secondary outcomes. Pre-definition of outcome reduces the risk of selective outcome reporting. The primary 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 in large part on the effects of the interventions on these outcomes. See Handbook 5.4.2
- Keep the total number of outcomes selected for inclusion in the review as small as possible. Choose outcomes that are relevant to stakeholders such as consumers, health professionals and policymakers. Avoid trivial outcomes and biochemical, interim and process outcomes, but consider the importance of resource-use outcomes. Cochrane reviews are intended to support clinical practice and policy and should address outcomes that are important to consumers. These should be specified at protocol stage. Where they are 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 on 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. See Handbook Chapter 3.2.4
- Define in advance details of what are 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; however, be difficult to pre-define adverse effects. See Handbook 5.4.1
- Define in advance how outcome measures will be selected when there are several possible measures (e.g. multiple definitions, assessors or scales). Pre-specification guards against selective outcome reporting and allows users to confirm that choices were not overly influenced by the results. A pre-defined hierarchy of outcomes measures may be helpful. It may; however, be difficult to pre-define adverse effects. A rationale should be provided for the choice of outcome measure. See Handbook 5.4.1

- Define in advance the timing of outcome measurement. Pre-specification 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 pre-specified 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.

Primary outcomes

- The review's primary outcomes should normally reflect at least one potential benefit and at least 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.
- The primary outcomes should appear in your Summary of findings table

Secondary outcomes

- Non-primary outcomes should be listed here. The total number of outcomes addressed should be kept as small as possible.

Search methods for identification of studies

- No text should appear under this heading
- Refer to MECIR PR17-PR21
- See Handbook Chapter 4

Electronic searches

- The bibliographic databases searched, the dates and periods searched and any constraints such as language should be stated. The full search strategies for each database should be listed in an appendix to the review. If a CRG has developed a specialized register of studies and this is searched for the review, a standard description of this register can be referred to, but information should be included on when and how the specialized register was most recently searched for the current version of the review and the search terms used should be listed.

The text below is a suggestion/checklist. Authors are welcome to change the wording or add extra information about handsearching, extra databases etc.

We will search for studies as described in the Cochrane Handbook of Systematic Reviews of Interventions Chapter 4 (Higgins 2019). There will be no language, publication year or publication status restrictions.

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (latest Issue)
- MEDLINE (Ovid SP, 1946-Date)
- EMBASE (Ovid SP, 1974-Date)
- Web of Science (1945-Date)
- [And other relevant databases (e.g., CINAHL, PsycInfo, Biosis, Scopus, LILACS, etc.)]

We developed a draft search strategy in MEDLINE. The search strategy can be found in Appendix 1 (INSERT LINK) and it will be modified appropriately for the other databases.

Searching other resources

We will check the bibliographic references and citations of relevant studies and reviews for further references to trials. We will also search ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) and ISRCTN (http://www.isrctn.com) for unpublished and ongoing studies, Open Grey (http://opengrey.eu/) for grey literature and Google Scholar for additional trials. When necessary we will contact trial authors for additional information.

Data collection and analysis

No text appears under this heading

Selection of studies

The method used to apply the selection criteria. Whether they are applied independently by more than one author should be stated, along with how any disagreements are resolved. See Handbook Chapter 4 and MECIR PR9-16.

Data extraction and management

The method used to extract or obtain data from published reports or from the original researchers (for example, using a data collection form). Whether data are extracted independently by more than one author should be stated, along with how any disagreements are resolved. If relevant, methods for processing data in preparation for analysis should be described. See Handbook Chapter 6, and MECIR PR22-40

Assessment of risk of bias in included studies

- 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 overall judgements of low risk, high risk and unclear risk of bias.
- Pre-defining 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, the Cochrane Risk of bias tool (note Risk of bias-2 is now available as outlined in the Handbook) 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 Chapter 8, and MECIR C52-60.
- Whether methods are applied independently by more than one author should be stated, along with 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

Measures of treatment effect

- 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). Pre-defining 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 Chapter 6 and MECIR R76-R99

Unit of analysis issues

- Special issues in the analysis of studies with non-standard designs, such as cross-over trials and cluster-randomized trials, should be described.
- Unit of analysis issues are discussed in Handbook Chapter 6.2
- Some non-standard designs are discussed in detail in Chapter 16, including cluster-randomized trials (Chapter 6.2.2), cross-over trials (Chapter 6.2.3), and studies with multiple intervention groups (Chapter 6.2.9). Non-randomized studies are discussed in Chapter 24.

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 in Handbook Chapter 10.12.

Assessment of heterogeneity

- Approaches to addressing clinical heterogeneity should be described, along with how the authors will determine whether a meta-analysis is considered appropriate. Methods for identifying statistical heterogeneity should be stated (e.g. visually, using I^2, using a chi-squared test).
- Assessment of heterogeneity is discussed in Handbook Chapter 10.10.

Assessment of reporting biases

- This section should describe how publication bias and other reporting biases are addressed (for example, funnel plots, statistical tests, imputation). 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 Handbook Chapter 13.

Data synthesis

- The choice of meta-analysis method should be stated, including whether a fixed-effect or a random-effects model is used. 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 in Handbook Chapter 10.

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.
- See Handbook Chapter 10.11.3 and MECIR PR36

Sensitivity analysis

- This should describe analyses aimed at determining whether conclusions are robust to 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.
- See Handbook Chapter Chapter 10.14 and MECIR PR32.

Summary of findings table and GRADE

- You need to decide which outcomes will appear in your SOF table and state them here.
- You should plan in advance the methods to be used for summarizing the findings of the review, including the assessment of the quality of the body of evidence.
- You should specify which outcomes will be included, and which comparisons and subgroups will be covered (if appropriate).
- You should predefine the Methods for 'Summary of findings' tables particularly with regard to choice of outcomes, 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 should generally not include surrogate or interim outcomes. These outcomes should not be chosen on the basis of any anticipated or observed magnitude of the effect, or because they are likely to have been addressed in the studies to be reviewed.

- See Handbook Chapter 14 for information on completing the 'Summary of findings' tables and grading the certainty of evidence.

Acknowledgements

You can acknowledge anyone who has helped you in this section. We will provide guidance on acknowledging the editorial team closer to publication.

Contribution of authors

- Complete the template copied and pasted in the protocol (see MECIR PR42)

Declarations of interest

- You need to review Cochrane's Conflict of Interest Policy; you will find it here.
- Please follow MECIR PR43 for reporting Declarations of interest and ensure that, at minimum, all disclosures stated in your Conflict of interest forms are included in these statements.

References/Additional references

- See: Cochrane Style Manual - References for instructions on the presentation of references

Appendices

- At minimum, please make sure you provide a copy of your MEDLINE search in *Appendix 1*. (Send a copy of your proposed MEDLINE search terms to our Information Specialist, Janne Vendt, (janne.vendt@regionh.dk) and check with her that your search is correctly constructed. Please be aware that Janne will not design your search but will check that your search is adequate and provide assistance as required.
- Insert a copy of your data extraction form in *Appendix 2* and link to the text (contact Jane if you would like to use a copy of our template form)