# HomeCochrane Fertility Regulation

**Guidance for Conducting Fertility Regulation Group Protocols**

This guidance provides suggested language that can be used verbatim in protocols submitted for FRG Cochrane Reviews. Apart from the text for the description of the search strategy, which must be verbatim, please consider each section in relation to your review question. It may be necessary to revise the sample language in this template to address issues specific to your review topic.

# **TITLE REGISTRATION**

Systematic reviews following Cochrane methods are designed to answer a specific question or set of related questions. They are not intended to provide a general overview of evidence in a topic area.

Before beginning a review, the study team should develop a clear statement of the review objective. In some cases, as in an update to a review, this will be partly or entirely informed by the previous review. Updates to previous reviews may require refinement of the objective as the evidence on a research topic develops and matures over time.

The review objective, or question the review sets out to answer should be important to answer for the people experiencing the condition or problem, clinicians, policy makers, or some combination of these stakeholders.

Cochrane reviews can be focused or broad in scope. Generally focused reviews are easier to carry out. Although more time consuming, broad reviews can be valuable for some topics. The specific questions to be answered must be clearly defined whether the scope is focused or broad. In some cases, with an experienced review team, an overview of reviews can be undertaken to review a set of reviews addressing related questions with implications for a clinical or policy area.

<https://community.cochrane.org/review-production/production-resources/proposing-and-registering-new-cochrane-reviews>

**Develop a clear and concise title for the review**

As much as possible make the title clear, concise and descriptive of the intervention, outcome and population that are the focus of the review. Note that titles for updated reviews can be revised to improve clarity and to adhere to this guidance. Some variability based on the idiosyncratic nature of different topics is allowed, and the population does not always need to be stated if it is clearly implied by the intervention and outcome.

The titles of Cochrane reviews all follow a similar logic and should fit one of the following forms:

1. [Intervention] for [health problem]

2. [Intervention A] versus [Intervention B/Control] for [health problem]

3. [Intervention] for [health problem] in [participant group/location]

***Effectiveness reviews*** evaluate whether an intervention or set of related interventions work to address clinical or population health outcomes. The structure of the title should generally have this format: [Intervention] for [Condition or Outcome] among/in [Population]

EXAMPLES:

Antibiotics for incomplete abortion

Hormonal contraception for women at risk of HIV infection

***Comparative effectiveness reviews*** evaluate which of two or several interventions are best for addressing clinical or population health outcomes. The structure of the title should generally have this format: [Intervention A] or/versus [Intervention B] for [Condition or Outcome] among [Population]

EXAMPLES:

Progestin IUDs versus Copper IUDs for emergency contraception

Doctors or mid-level providers for abortion

Combined hormonal versus nonhormonal versus progestin-only contraception in lactation

**Clearly define the main objective of the review**

Define the main objective of the review, including participants, interventions, comparators, and outcomes, where appropriate in a single concise sentence.

To assess the effects of [intervention or comparison] for [health issue/healthcare system] for/in [types of people, disease or issue and setting if specified].

Any secondary objectives should be expressed in terms that relate to the population(s), intervention comparison(s) and, where appropriate, outcomes of interest. Consider in advance whether issues of equity and relevance to specific populations (e.g. low-socioeconomic groups, low- or middle-income regions, women, children and older people) are important to the review.

EXAMPLES:

*Primary Objective*: Examine the effectiveness of decision aids when used in contraception counselling, both on contraceptive choice and use.

*Secondary Objective*: Compare the effectiveness of clinic-based and out-of-clinic interventions.

*Primary Objective*: To compare the efficacy and safety of Chinese Herbal Medicine with other surgical and or medical methods for induced abortion in early pregnancy (before 14 weeks’ gestation).

See: <https://training.cochrane.org/handbook/current/chapter-03>

# **REVIEW PROTOCOL**

Cochrane review protocols should comply with the most recent *Cochrane Handbook for Systematic Reviews of Interventions* (version 6, 2019) and Methodological Expectations of Cochrane Intervention Reviews (MECIR) Standards. The standard and suggested text provided here was developed using these resources.

<https://training.cochrane.org/handbook/current>

<https://community.cochrane.org/mecir-manual>

## BACKGROUND

### Description of the condition

Describe the condition being addressed and its significance. This might include information about the biology, diagnosis, prognosis, prevalence, incidence and burden of the condition. This section should be brief and focused, without extraneous information. The context provided in the background should be central to the question the review will aim to answer.

See [Section 3.3.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-iii#section-iii-3-2)

### Description of the intervention

Describe the intervention(s) placing it in the context of any standard or alternative interventions. Please note that standard practice may vary widely according to context. State the role of the comparator intervention(s) in standard practice. For drugs please include basic information on clinical pharmacology such as dose range, metabolism, selective effects, half-life, duration and any known interactions with other drugs. For more complex interventions, such as behavioral or service-level interventions, a description of the main components should be provided (see [Chapter 17 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-17)).

See [Section 3.3.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-iii#section-iii-3-2)

### How the intervention might work

Explain the known or theorized mechanism for the intervention effect being evaluated. Discuss issues of health and social equity and the potential importance of the intervention for specific subpopulations, as relevant.

See [MECIR C4](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/setting-research-question-inform-scope-review-c1-c4) and [Section 2.4.3 Cochrane Handbook version six](https://training.cochrane.org/handbook/current/chapter-02#section-2-4-3).

### Why it is important to do this review

Highlight the importance of the review and important stakeholders likely to be affected by the intervention. These might include patients, caregivers, health care providers, and others. Please refer, amongst other points, to national and international guidelines in this section.

*See* [MECIR PR3-PR4](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/background-pr3-pr4); [Section 3.3.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-iii#section-iii-3-2)

## OBJECTIVES

Clearly state the review objectives following the guidance provided above for the title registration. Sometimes it may be evident during the drafting of the protocol, as authors get into the details of the review, that a change to the wording of the objectives is needed. It is ok for the objectives in the published protocol to differ from what was included in the title registration. Use a list format to present each of the research questions you will plan to answer and the comparisons that will be assessed to address them.

*See* [MECIR C1-C4](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/setting-research-question-inform-scope-review-c1-c4)*;* [MECIR PR5-PR8](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/objectives-pr5-pr8)*;* [Section 3.3.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-iii#section-iii-3-2)

## METHODS

### Criteria for considering studies for this review

### Types of Studies

Historically, Cochrane Reviews have focused heavily on RCT literature, but in recent years efforts to support and develop guidance for reviewing evidence from non-randomised studies of interventions (NRSI) has expanded. Authors that plan to include NRSI in their reviews should read the recent guidance in the Cochrane Handbook ([Section 3.3.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-03#section-3-3-2)). In addition, authors should be prepared for some additional complexity in the review process when NRSI are included (e.g. risk of bias assessments using ROBINS-I).

Specify the types of studies you will consider for your review and include detail of the precise nature of the design features of the included study type(s). State if you plan to include:

* RCTs randomised at the level of the participant (parallel and or cross over)
* RCTs randomised at the cluster level (cluster RCTs)

If you are considering including parallel-arm RCTs with allocation decided by an approximation of randomization (e.g. allocation by Patient ID Number) (quasi-RCTs) provide a justification for inclusion.

The review should also specific whether crossover trials or cluster randomized trials will be included. Characteristics of the intervention or outcomes for the topic may preclude these designs. For example, crossover trials are not valid if success or failure of the treatment does not allow for crossover (e.g. pregnancy outcome).

**Suggested language:**

*We will include parallel RCTs including those randomized at the individual or cluster level, and will not include cross-over trials because this is not feasible/ethical for studies of the intervention evaluated in this review [USUALLY THE CASE FOR REVIEWS SUBMITTED TO THE FRG]. Trials of interventions with allocation using an approximation of randomization (e.g., patient record number) will also be considered for inclusion because randomization of participants to the intervention [SPECIFY] examined in this review is [unethical, uncommon, not feasible – provide reason for expanding to nonrandomized trials].*

*We will include studies irrespective of their publication status and language of publication.*

*Deciding whether to include NRSI and what designs to include*

Authors planning to include NRSI should review the relevant Cochrane Handbook chapter to become familiar with additional requirements and considerations for conducting such a review (<https://training.cochrane.org/handbook/current/chapter-24>).

As noted above, many of the topics supported by the FRG Cochrane group will have limited available RCT evidence to address review objectives. RCTs are the optimal evidence for answering most clinical questions with lower risk of bias than nonrandomized studies of interventions (NRSI). Authors should carefully consider the purpose and limitations of a review that includes NRSI. Such reviews pose unique challenges and are often more time consuming and complex to produce. Moreover, even when NRSI are included, the review objectives may not be met due to shortcomings in the evidence for drawing valid inferences about intervention effectiveness or safety.

In some cases, a review that formally includes and analyzes a very small number of RCTs can make an important contribution to the literature by outlining the need for additional research and highlighting important context from the broader literature in the background and discussion text. Authors of such reviews can set the stage for future updates as research in the area develops.

In other cases, the need for a full accounting of the RCT and NRSI evidence to answer an important clinical or policy questions justifies the decision to broaden the review to include studies other than RCTs. For many of the topics authors review in the Fertility Regulation Group, NRSI may provide the only or best available evidence on a topic.

There are two key reasons outlined in the Cochrane Handbook that can be used to justify inclusion of NRSI evidence (<https://training.cochrane.org/handbook/current/chapter-24#section-24-1-1>).

*To provide evidence of the effects (benefit or harm) of interventions that can feasibly be studied in randomized trials, but for which available randomized trials address the review question indirectly or incompletely.*

*To provide evidence of the effects (benefit or harm) of interventions that cannot be randomized, or that are extremely unlikely to be studied in randomized trials. Such non-randomized evidence might address, for example, population-level interventions or interventions about which prospective study participants are likely to have strong preferences, preventing randomization.*

Two that may also sometimes be reasonable to invoke for FRG topics are as follows:

*To examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available NRSI. The findings of a review of NRSI may also be useful to inform the design of a subsequent randomized trial.*

*To provide evidence of the effects (benefit or harm) of interventions that can feasibly be studied in randomized trials, but for which only a small number of randomized trials is available (or likely to be available).*

To make decisions about the specific NRSI study designs to include in the review, **authors should scan the evidence on the intervention topic to understand the scope of the available NRSI evidence**. This should be done after registering a title but in advance of writing a protocol. This will allow review authors to confirm that relevant NRSI exist and to specify NRSI with the most appropriate study design features.

As much as possible define specific design characteristics that will be included rather than using broad study design labels to describe the studies that will be included. It is important to provide details that can be used to clearly determine eligible study designs. Descriptors of study design features that will be allowed or excluded are most helpful. For example, types of comparators allowed (historical or concurrent) or sources of cases and controls (nested in prospective cohort study, matched).

Instead of quasi-randomized studies 🡪 e.g. intervention trials that involve allocation by a non-random process such as alternating patients or clinic days.

Instead of observational studies 🡪 e.g. prospective cohort studies with a concurrent comparison group, cohort studies with concurrent or historical comparison groups, case-control studies nested in a prospective cohort.

**For additional resources to think through different potential study designs to consider for inclusion see the Checklist in the Cochrane Handbook provided in** [**Box 24.2.a**](https://training.cochrane.org/handbook/current/chapter-24#section-24-2) (Reeves et al 2017).

**Suggested language for a review that includes NRSI:**

*We will include randomized controlled trials and nonrandomized studies of interventions. While randomized control trials represent the most rigorous type of study for addressing questions of efficacy and safety, for this topic nonrandomized studies will be included because [provide reasoning – see above] for this clinical intervention, the efficacy and safety outcomes of interest are very rare and the number of participants willing to be randomized to [X] may be limited. This reduces the feasibility and likelihood of adequately powered randomized trials. We do not expect to find adequate trial evidence to address the review objectives and nonrandomized studies provide the best available data for testing comparisons between [X] and novel interventions such as [Y].*

*We will include studies irrespective of their publication status and language of publication.*

*[LIST SPECIFIC STUDY DESIGNS THAT WILL BE INCLUDED – EXAMPLES FOLLOW]*

*In addition to RCTs, we will include trials of interventions that allocate individuals or clusters to intervention and control conditions using nonrandom processes.*

*We will include cohort studies that compare individuals or clusters exposed to the intervention to a comparable group of unexposed individuals or clusters over the same time period (e.g., comparative cohort, case-control studies nested in a prospective cohort).*

*Cohort studies that compare individuals or clusters exposed to the intervention over one time period to a comparable group of unexposed individuals or clusters from another time period (e.g., before after study designs, interrupted time series).*

### Types of Participants

Predefine unambiguous criteria for participants. Define in advance how you will handle studies that include only a subset of relevant participants. Restrictions to study populations must be based on sound rationale and described here. Define age cut-off for adults/adolescents/young adults/children/infants. See [MECIR C5-6](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/setting-eligibility-criteria-including-studies-review-c5-c13); [MECIR PR11](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/criteria-considering-studies-review-pr9-pr16); [Section 3.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-03#section-3-2)

When defining the inclusion criteria for study participants, in some cases it may be important to establish a strict rule where studies with any participants falling outside of the category will be excluded. For example, a study of pain outcomes for induced abortion procedures might exclude any studies that include procedures for miscarriage. In other cases, the review may focus on a specific population, but will not exclude studies with a small number of participants outside of that group. Sensitivity analyses can be undertaken to see if the inclusion of these individuals makes a difference in the effects estimated. The cut point is likely to be anywhere from 5% to 20% of participants outside of the population of interest, and will depend on the clinical issue and the extent to which it is expected that the criteria could influence the findings or limit the available evidence.

EXAMPLE: We will seek studies conducted among pregnant individuals of any age obtaining a medication abortion, between 8 and 13 weeks of gestation. Studies will not be excluded, however, if fewer than 10% of participants obtained abortions outside of this range.

### Types of Interventions

List both the interventions and the comparators you will include in your review. Pay attention to active comparator interventions (e.g. a different variant of the same intervention, a different drug, or a different kind of therapy). If you plan more than one comparison, define each one, preferably as a list (e.g. statin versus placebo; warfarin plus aspirin versus warfarin). Indicate any specific aspects related to the intervention or comparator e.g. route of administration, duration of intervention, frequency that define the comparisons. For multi-component or complex interventions define any common or core features that will define that intervention. [Section 3.2.2 Chapter handbook version six](https://training.cochrane.org/handbook/current/chapter-03#section-3-2-2). If co-interventions may be present alongside the main comparisons of interest in the evidence being reviewed, state how this will be managed. [Section 3.2.3.1 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-03#section-3-2-3-1)

Provide a complete description of the comparators that are valid for addressing the review objective. For example, reviews aimed at establishing the effectiveness and safety of a clinical intervention would likely focus on comparisons to placebo, no treatment, usual care, or attention control comparators, depending on the topic. Where usual care comparators are to be included, a clear definition of what will be accepted as a usual care comparison should be provided. Reviews comparing active interventions (different clinical protocols, drugs, care delivery models) should specify each of the relevant comparisons to be evaluated in a list.

**Suggested language:**

*We will include trials comparing [intervention] with [usual care/other].*

*The comparisons for this review will be:*

* *XX compared with XX*
* *XX compared with XX*
* *XX compared with XX*

EXAMPLES:

Telemedicine delivery of medication abortion versus usual care delivery of medication abortion in a clinic setting without telemedicine delivery of services

Pain medication 1 versus Pain medication 2

Pain medication 2 versus Pain medication 3

*See* [MECIR C7](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/setting-eligibility-criteria-including-studies-review-c5-c13);[MECIR PR12](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/criteria-considering-studies-review-pr9-pr16); [Section 3.2.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-03#section-3-2-2)

### Types of Outcome Measures

A small number of critical/important outcomes should be specified, meaning as few as possible and no greater than seven. At least one potential benefit and one potential harm of the intervention should be included as critical outcomes. Keep secondary outcomes to a minimum and focus on clinical outcomes rather than lab findings. Each critical/primary outcome will be assed for overall risk of bias and GRADE table assessment. It is important to select outcomes that are clinically meaningful, valid, and more commonly and consistently reported in the literature being reviewed. Health outcomes that are likely to be objectively assessed and occur regardless of the health care setting or clinical variation in evaluations should be prioritized. Published validated measures of patient reported outcomes are preferable to study-specific measures created by research teams. Composite outcomes (e.g. major adverse events) are not generally acceptable measures for critical/primary outcomes, as they are likely to be defined differently across studies and at risk for double counting. Instead, abstract the counts of specific important outcomes.

Define in the protocol details what will be included as acceptable outcome measures (e.g. differing scales, time-points), and state a preference order when there are several possible measures.

Check the COMET database (<http://www.comet-initiative.org/studies/>) to see if there are any relevant core outcome sets for the topic.

Reporting one or more of the outcomes listed in this section of the protocol is not an inclusion criterion for the review. Where a published report does not appear to report one of these outcomes, review authors should access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. Relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, will be included in the review as part of the narrative.

EXAMPLES

Primary outcomes

1. Live birth or ongoing pregnancy

a. Live birth is defined as delivery of a live fetus after 20 completed weeks of gestation

b. Ongoing pregnancy is defined as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed with ultrasound

2. Multiple pregnancy

Secondary outcomes

3. Clinical pregnancy, defined as evidence of a gestational sac, confirmed by ultrasound

4. Any adverse event (including miscarriage, bleeding, drug reactions), reported either as a composite measure or separately

5. Quality of life. If studies report more than one scale, preference will be given to the SF-36, then other validated generic scales, and finally condition-specific scales

*See:* [MECIR C8](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/setting-eligibility-criteria-including-studies-review-c5-c13); [MECIR C14-C18](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/selecting-outcomes-be-addressed-studies-included-review-c14-c18); [MECIR C40](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/selecting-studies-include-review-c39-c42);[MECIR PR13-PR16](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/criteria-considering-studies-review-pr9-pr16); [Section 3.2.4 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-03#section-3-2-4);[Section 8.7 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-08#section-8-7)

## Search methods for identification of studies

\*The text in this search section is drafted by the FRG Information Specialist (Robin Paynter), no further editing is required from authors. Robin will draft the search strategy and ask for author input before running the search. Robin will run the literature search, import the results into Covidence for literature review and edit this section as needed.

The Fertility Regulation Group Information Specialist will conduct a search for all published, unpublished, and ongoing studies, without restrictions on language or publication status. The search strategies for each database will be modelled on the search strategy designed for MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), available in Appendix 1.

### Electronic searches

We will search the following databases from their inception:

The electronic bibliographic databases that you will search and include, as necessary, the platform you will use to search. For example:

* EBM Reviews Ovid - Cochrane Central Register of Controlled Trials
* MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily)
* Embase.com
* CINAHL
* LILACs http://lilacs.bvsalud.org/en/
* Global Health Ovid
* Scopus

We will search the following trials registries:

* The World Health Organization International Clinical Trials Registry Platform [www.who.int/trialsearch](http://www.who.int/trialsearch)
* ClinicalTrials.gov [www.clinicaltrials.gov](http://www.clinicaltrials.gov/).

We will search the following grey literature sites:

* Guttmacher Institute <https://www.guttmacher.org/united-states/abortion>
* International Planned Parenthood Federation <https://www.ippf.org/>
* Ibis Reproductive Health <https://ibisreproductivehealth.org/>
* Women on Waves <https://www.womenonwaves.org/>
* Marie Stopes International <https://www.mariestopes.org/>
* Population Council <https://www.popcouncil.org/>
* Population Services International <https://www.psi.org/>
* Ipas <https://www.ipas.org/> ]

### Searching other resources

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant studies. We will contact experts/organizations in the field to obtain additional information on relevant studies. If necessary, we will contact authors of included studies for data clarification and further information. We will consider adverse effects described in included studies only.

## Data collection and analysis

### Selection of studies

Describe how decisions on which studies to include from the search results will be made, describe the process by stating which reviewers (at least two) will be involved and whether they worked independently and how you will deal with disagreements.

**Suggested language:**

*We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Two reviewers [initials here] will independently screen titles and abstracts for inclusion. We will retrieve the full-text study reports/publication and two reviewers [initials here] will independently screen the full-text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author [initials here]. We will list studies that initially appeared to meet the inclusion criteria but that we later excluded in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).*

### Data extraction and management

Ideally, the data extraction form should be piloted with a small number of studies.

**Suggested language:**

*We will use a standard data collection form for study characteristics and outcome data; we will pilot the form on at least one study in the review. Two reviewers [initials here] will independently extract the following study characteristics from the included studies:*

* + - *Methods: study design, number of study centers and location, study setting, withdrawals, date of study, follow-up, approach to adjustment for design effects or confounding.*
    - *Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria, other relevant characteristics.*
    - *Interventions: intervention components, comparison, fidelity assessment.*
    - *Outcomes: events, means, relative effects, time points reported, adjusted effect estimates and information about the confounders and design effects accounted for, intra-cluster correlations (ICCs) for studies with clustering*
    - *Notes: funding for trial, notable conflicts of interest of trial authors, ethical approval [add to this list as required].*

*Two reviewers [initials here] will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author [initials here].*

### Assessment of Risk of Bias in included studies

The approach to conducting the Risk of Bias assessment can be indicated using standard text, with some additional considerations if including study designs that require other tools or adaptations of the standard tools used for trials and NRSI.

For studies including parallel arm RCTS, crossover RCTs, or cluster RCTS, RoB2 should be used, or domains added to RoB1. Note that 'Quasi' RCTs can sometimes be assessed for bias using the RoB2 tool, but for studies where allocation may include features related to prognosis, or disease progression, you may need to assess bias using the ROBINS-I tool as it will be better suited to assess issues related to the potential for confounding. See FRG editors for guidance or see sections [23.1.2](https://training.cochrane.org/handbook/current/chapter-23#section-23-1-2) and [23.2.3](https://training.cochrane.org/handbook/current/chapter-23#section-23-2-3) in the Cochrane handbook version six.

Pre-specify whether you are interested in quantifying the effect of **assignment** to the interventions at baseline, regardless of whether the interventions are received as intended (the ‘intention-to-treat effect’); or the effect of **adhering to** the interventions as specified in the trial. If the effect of adherence is sought, this focus needs to be justified. For most research questions authors will be expected to assess the effect of assignment to the intervention. For some topics, the effects of both assignment and adherence may be sought, with the biases related to adherence analyses carefully considered.

**Suggested language:**

*Two [or more] review authors (insert initials here) will independently assess risk of bias for each study. We will resolve any disagreements by discussion or by involving another author (insert initials here).*

*If using ROB:*

*We will assess the risk of bias in randomized trials using the Cochrane RoB tool (Higgins 2020a;* [*Higgins 2011*](https://revman.cochrane.org/416747616972327341)*). Our effect of interest will be the effect of assignment, also known as the ‘intention to treat’. The trials will be evaluated for risk of bias in the following domains:*

* *Random sequence generation*
* *Allocation concealment*
* *Blinding of participants and personnel*
* *Blinding of outcome assessment*
* *Incomplete outcome data*
* *Selective outcome reporting*
* *Other bias*

*The “other bias” domain will be used to assess bias related to cross over study designs.*

*We will judge each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient reported pain scale).*

*If using ROB2:*

*We will assess the risk of bias for key outcomes results of randomized trials using the Cochrane ROB2 tool (Sterne 2019). Our effect of interest will be the effect of assignment, also known as the ‘intention to treat’. The of the outcomes defined in this protocol will be assessed for risk of bias. The following domains will be assessed on the basis of answers to signaling questions:*

*(1) bias arising from the randomization process*

*(2) bias due to deviations from intended interventions*

*(3) bias due to missing outcome data*

*(4) bias in measurement of the outcome*

*(5) bias in selection of the reported result*

*An additional domain is included for cluster-randomized trials*

*(1b) Bias arising from identification or recruitment of individual participants within clusters*

*We will use the variants of RoB 2 for cluster RCTs and cross-over RCTs if we identify eligible trials with these study designs.*

*For each outcome we will use the signaling questions to categorize each domain as low risk of bias, some concerns, or high risk of bias. Answers to the signaling questions will be recorded on the ROB2 Excel tool and made available in an online repository. We will summarize the risk of bias judgments across different studies for each of the domains for each prespecified outcome. For each study an overall judgment will be derived from the tool, as follows:*

* *Low risk of bias: the study is considered to show a low risk of bias;*
* *Some concerns: a few concerns are expected to be associated with the study in at least one domain, but not warranting categorization as a study with a high risk of bias for any domain;*
* *High risk of bias: the study is considered to be at high risk of bias in at least one domain; or a few concerns with regard to multiple domains are observed in the study such that these concerns significantly lower confidence in the study results.*

*If NRSI included:*

*We will assess the risk of bias for key outcomes from NRSI using the ROBINS-I instrument (Sterne 2016; Higgins 2020b). To conduct the assessment of bias due to confounding, we will be attentive to the potential for the following confounding factors to be of concern in the evidence on this topic: [LIST POTENTIAL CONFOUNDERS THAT COULD INFLUENCE TRIAL RESULTS IF NOT ACCOUNTED FOR IN THE STUDY DESIGN]. Using the ROBINS-I tool which includes signaling questions for assessing different potential sources of bias, we will evaluate the following domains:*

* *Pre-intervention*
  + *Bias due to confounding*
  + *Bias in selection of participants into the study (selection bias)*
* *At intervention*
  + *Bias in classification of interventions (information bias)*
* *Post-intervention*
  + *Bias due to deviations from intended interventions (confounding)*
  + *Bias due to missing data (selection bias)*
  + *Bias in measurement of outcomes (information bias)*
  + *Bias in selection of the reported result (reporting bias)*

*We will assess the risk of bias for the outcomes of the included trials that will be included in our Summary of Findings table (*[*Section 8.2.1 Cochrane handbook version six*](https://training.cochrane.org/handbook/current/chapter-08#section-8-2-1)*).*

*Answers to the signaling questions will be recorded and made available in an online data repository (e.g. srdr.ahrq.gov, figshare.com, datadryad.org). Answers to the signaling questions will inform judgments about the risk of bias for each domain as assessed for each outcome obtained from each study. We will summarise the risk of bias judgments across different studies for each of the domains for each prespecified outcome.*

AFTER DESCRIBING RISK OF BIAS TOOLS AND APPROACH USED:

*Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will not exclude studies on the grounds of their risk of bias but will clearly report the risk of bias when presenting the results of the studies. When summarizing the evidence on treatment effects for different outcomes, we will consider the risk of bias for the studies that contributed to analyses for that outcome.*

### Applying risk-of-bias assessments in this review

**Suggested language:**

*We will take into account the risk of bias for the studies that are used to estimate intervention effects. We will provide figures to illustrate the risk of bias. We will conduct sensitivity analyses (see Sensitivity Analysis section below) to assess whether estimated effects differ when high risk of bias studies are excluded from analyses. The risk of bias assessment will inform the GRADE and Summary of Findings tables.*

*See* [MECIR C20](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/planning-review-methods-protocol-stage-c19-c23): [MECIR C52-C60](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/assessing-risk-bias-included-studies-c52-c60); [MECIR PR27-PR28](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40); [Chapter 7 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-07): [Chapter 8 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-08)

### Measures of treatment effect

State the treatment effects that you expect to analyze and indicate that you will ensure all scales are measuring their effect in the same direction and you will convert any that run counter to others (e.g. a high value for a scale indicates a poorer outcome for the participant and a low value indicates a good outcome). Explain circumstances where you would use SMD, and where you would use MD. For all study designs, but especially for clustered trials and reviews including NRSI, include a statement indicating that adjusted effect estimates will be reported along with the variables used for the adjustment.

**Suggested language:**

*We will report the effects of interventions for dichotomous outcomes as risk ratios [and/or odds ratios] with 95% confidence intervals and for continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals. Outcomes adjusted for confounders or design effects (e.g., clustering) will be reported and, where possible, used for meta-analysis.*

*[Include the following sentences only if relevant for the specific topic: Where studies report count data - the number of events rather than the number of people who experienced an event - we will use the number of events and number of person-years to calculate rate ratios (Chapter 6.7 of the Cochrane Handbook).]*

*We will use SMDs when different scales are used to measure the same outcomes, necessitating the standardization of the results of the studies to a uniform scale before they can be combined. Data presented as scales will be reported so that there is consistency in the direction of effects. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study, thus studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements. To interpret the SMD, we will use the Cohen’s effect size rubric where 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988). If possible, we will express the study SMDs using a recognizable and standard metric used by some of the included studies or employ other strategies to aid interpretability outlined in* [*Section 15.5 Cochrane handbook version 6*](https://training.cochrane.org/handbook/current/chapter-15#section-15-5)*.*

*For studies reporting results that are not provided in a format that can be directly entered into meta-analysis – we will use guidance provided in* [Chapter 6 of the Cochrane Handbook (version](https://training.cochrane.org/handbook/current/chapter-06) six) *to convert the data to the necessary format.*

### Unit of analysis issues

There are three main types of unit of analysis considerations to address in the protocol that may or may not be present in the included literature. The protocol should state whether each of the following unit of analysis issues will be present, and how they will be dealt with in analyses.

* 1. groups of individuals were randomized together to the same intervention (i.e. cluster-randomized trials);
  2. individuals underwent more than one intervention (e.g. in a crossover trial, or simultaneous treatment of multiple sites on each individual);
  3. and there were multiple observations for the same outcome (e.g. repeated measurements, recurring events, measurements on different body parts).

Note that RCTs with three or more arms or with measurements at multiple time points represent cases of repeated measurement. If these types of trials may be included in the review, explain your method to avoid double-counting in the meta-analysis.

**Suggested language:**

*We will perform the primary analysis per individual randomized.[Include the following if cluster-randomized trials will be included: We will abstract information on the study design and unit of analysis for each study, indicating whether clustering of observations is present due to allocation to the intervention at the group level or clustering of individually randomized observations (e.g. patients within clinics). Available statistical information needed to account for the implications of clustering on the estimation of outcome variances will be abstracted, such as design effects or intra-cluster correlations, and whether the study adjusted results for the correlations in the data. In cases where the study does not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size following Cochrane guidance (Higgins 2020b). Where possible, we will derive the intra-cluster correlation (ICC) for these adjustments from the trial itself, or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.]*

*If any trials have multiple arms that are compared against the same control condition that will be included in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, select one pair of interventions and exclude the others.*

*In the meta-analysis and data synthesis, we will only include the first-phase data from cross-over trials.*

**More detailed text for handling of clustered and multi-arm trial data, for reviews expecting this type of evidence to be included:**

*Where cluster-RCTs have not adjusted their results for the effect of the cluster design, we will adjust the sample sizes using an estimate of the intra-cluster correlation coefficient (ICC) as described in Sections 16.3.4 and 16.3.6 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Where possible, we will derive the ICC from the trial itself, or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.*

*When a multi-arm trial contributes multiple comparisons to a particular meta-analysis, we will either combine treatment groups or split the ’shared’ group as appropriate to avoid double counting.*

See: [MECIR C21](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/planning-review-methods-protocol-stage-c19-c23): [MECIR C47](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/collecting-data-included-studies-c43-c51) ; [MECIR C61](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73) ; [MECIR PR30](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40); ; [MECIR C70](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73); [MECIR PR29](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40): [Chapter 6 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-06)

### Dealing with missing data

*See:* [MECIR C47](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/collecting-data-included-studies-c43-c51)[MECIR C64](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73)[MECIR PR26](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40)[Section 6.3 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-06#section-6-3); [Chapter 13 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-13)

In this section, describe the methods you will use to identify additional and unpublished data.

**Suggested language:**

*We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data for those studies identified as abstract only.*

*We will calculate missing standard deviations or other necessary data using other data from the trial, such as confidence intervals, based on methods outlined in* [Chapter 6 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-06) *(*[Higgins 2020b](about:blankHiggins%202019b)*).*

*We will examine the possibility of selective non-reporting or under-reporting by noting the number of included studies that did not report key outcomes and therefore could not be included in our synthesis for key outcomes.*

*We will show all responses and data provided in the ’Characteristics of included studies’ table. Where we make any assumptions about missing data, we will report the potential impact in the ’Discussion’ section of the review.*

### Assessment of heterogeneity

Any kind of variability among studies in a systematic review may be termed heterogeneity. This includes **clinical diversity**, which covers variability in terms of participants, interventions etc. within studies; **methodological diversity** which includes variation in study design, outcome measurement tools used etc. and **statistical heterogeneity** which is variability in the numerical effect estimates and is a consequence of clinical diversity and methodological diversity. This section of the review protocol is primarily concerned with statistical heterogeneity, but reviews should summarize how studies vary clinically and methodologically to inform the review synthesis.

Data abstracted to describe clinical and methodological variability are usually covered in the Table of included studies. It can be helpful to provide an easily viewed overview of these in stand-alone tables.

**Suggested language:**

*We will describe the clinical diversity and methodological variability of the evidence in the review text and with study tables describing study characteristics including design features, population characteristics, and intervention details.*

*To assess statistical heterogeneity we will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap between confidence intervals. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the I² statistic to quantify inconsistency among the trials in each analysis. We will also consider the P value from the Chi² test to assess if this heterogeneity is significant (P < 0.1). If we identify substantial heterogeneity we will report the finding and explore possible explanatory factors using prespecified subgroup analysis.*

*A rough guideline will be used to interpret the I2 value rather than a simple threshold, and our interpretation will take into account an understanding that measures of heterogeneity (I2 and Tau) will be estimated with high uncertainty when the number of studies is small* ([Deeks 2020](about:blankDeeks%202019))*:*

* *0% to 40%: heterogeneity might not be important*
* *30% to 60%: may represent moderate heterogeneity\**
* *50% to 90%: may represent substantial heterogeneity\**
* *75% to 100%: considerable heterogeneity\**

*\*The importance of the observed value of I2 depends on (1) magnitude and direction of effects, and (2) strength of evidence for heterogeneity (e.g. P value from the Chi2 test, or a confidence interval for I2: uncertainty in the value of I2 is substantial when the number of studies is small).*

*See:* [MECIR C62](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73)*;* [MECIR C63](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73); [MECIR PR32](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40) *Section* [10.10.2](https://training.cochrane.org/handbook/current/chapter-10#section-10-10) *of the Cochrane Handbook version six.*

### Assessment of reporting biases

**Suggested language:**

*If we have enough studies available for meta-analysis to support a funnel plot (at least 10), we will create and visually inspect the funnel plot and run a formal statistical test for asymmetry, as proposed by* [Egger 1997](about:blankEgger%201997). *We plan to provide a funnel plot for [OUTCOME, OUTCOME], data permitting. For reviews with fewer studies eligible for meta-analysis the ability to detect publication bias will be largely diminished, and we will not the difficulty excluding the presence of publication bias. In the event that funnel plot asymmetry is observed in the evidence, we will discuss the potential for this to be attributed to small study effects and not just non-reporting bias.*

See: [MECIR C73](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73); [MECIR PR34](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40); [Chapter 13 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-13)

### Preparation for data synthesis and structure of comparisons [Optional section]

This subheading and section can be added to help organize reviews of complex interventions or involving multiple bodies of evidence. It is helpful to map out the review structure to guide the analysis of data when the conceptual framework is complex or involves several questions and comparisons within questions.

***Suggested language (optional – use only if this subsection will be included in the protocol)***

*DESCRIBE THE CONCEPTUAL FRAMEWORK OR LOGIC MODEL USED TO ORGANIZE THE REVIEW. We will first evaluate the effectiveness of X compared with X among … to establish the relationship between … and …*

*The studies that meet the review inclusion criteria will be organized to tabulate study characteristics needed to determine:*

* *which studies will answer each research question*
* *which studies have data available for numerical meta-analysis*
* *which studies have data that needs converting for meta-analysis*
* *which studies are suitable for a narrative synthesis*

*The approach to be taken for converting data found in studies to a format appropriate for meta-analysis will follow the methods described in* [Chapter 6 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-06).

*We will synthesize the characteristics of all studies that contribute to each comparison and present these in tabulated form in the review. See section* [Section 9.3](https://training.cochrane.org/handbook/current/chapter-09#section-9-3) and Table 9.3.b [Section 9.3.5 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-09#section-9-3-5).

*If relatively few studies are identified for the review, we will consider grouping synthesis-PICOs at a broader level. See* [Section 2.5.3 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-02#section-2-5-3) and [Section 9.3.4 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-09#section-9-4).

*Because it is not always possible to prepare pooled numerical meta-analyses for all data. We will undertake meta-analyses only where this is meaningful based on the comparability of the studies available (i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense). See section below for "Synthesis using other methods" when meta-analysis is not possible.*

*See* [Section 9.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-09).

### Data synthesis

The concept of data synthesis for systematic reviews includes both meta-analysis and synthesis without meta-analysis (SWiM; Campbell 2019). Both should be addressed in this section.

### Meta-analysis of numerical data

Please state whether you plan to use a random-effects or a fixed-effect model. Justify your choice of model. We would encourage authors to consider in advance whether it can be assumed that all studies in the meta-analysis are estimating the same intervention effect, or whether the studies are estimating intervention effects that follow a distribution across studies. See [Section 10.10.4.1 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-10#section-10-10-4-1) for an overview of the likely variations in intervention, population characteristics and methodological aspects that could lead to different intervention effects being estimated. Authors should not base their choice of model on the presence of heterogeneity according to particular threshold values of I2.

### Synthesis using other methods

It might not be possible to pool numerical data in a meta-analysis for one or more outcomes. See [Table 12.1.a Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-12#section-12-1) . For these reasons it is important to pre-specify the approaches you would take to present outcome data in these scenarios.

**Suggested language:**

*The intervention effect will be assessed separately for RCTs and for NRSI. We will undertake meta-analyses to estimate pooled effects when adequate comparable data are reported that can support statistical pooling. When necessary, comparable effect measures will be computed to support the inclusion of adjusted outcomes. For example, if adjusted odds ratios are reported in some of the included studies, odds ratios rather than relative risks will be computed to provide consistent numeric effects when pooling study results.*

*When skewed data are suspected based on the reporting of median and interquartile ranges, we will note the skewness and discuss the implication, but will not pool medians with means. For outcomes that cannot be statistically pooled, descriptive forest plots showing the individual study results will be presented to illustrate the range of effects reported.*

*The meta-analysis approach taken will be based on an evaluation of the clinical and methodological diversity of the included studies, as well as the statistical heterogeneity. Pooled analyses of outcomes with sufficient data will be generated using the Dersimonian and Laird random-effects technique. If study reported estimates adjusting for important confounders or design effects (e.g., clustering) are reported and appropriate to include in the pooled analysis, the inverse variance method will be used for meta-analysis. A fixed-effects estimate using the Mantel-Hanzel approach will be considered if the included studies can be assumed to estimate the same intervention effect, if the intervention effects are relatively consistent in direction and magnitude, and heterogeneity is low. The Mantel-Hanzel approach will also be considered if there is evidence of potential variation in outcome effects by study size (i.e. small study effects). For rare outcomes or trials with zero-count events, analyses using the Peto OR and other analytic approaches will be considered for the main analysis or to evaluate the stability of results in sensitivity analyses.*

*[FOR REVIEWS WITH PRIMARY OUTCOMES KNOWN TO BE RARE EVENTS, EXPAND ON AND ELEVATE DISCUSSION OF THE PETO OR FOR META-ANALYSIS]*

*Meta-analyses will be illustrated using a forest plot displaying effect estimates and 95% confidence intervals for both individual study effects and the pooled effect.*

*If the study data cannot be quantitatively summarized, we will follow guidance available for synthesis without meta-analysis outlined in Chapter 12 of the Cochrane handbook (v6) (McKenzie 2020). Our synthesis will avoid enumerating the statistical significance of effects of individual studies or focus only on individual studies that report statistically significant findings.*

See [MECIR C21](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/planning-review-methods-protocol-stage-c19-c23): [MECIR PR33](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40); [Chapter 12 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-12). [Webinar 1 on SWiM](https://training.cochrane.org/resource/narrative-synthesis-quantitative-effect-data-cochrane-reviews-current-issues-and-ways).

### Subgroup analysis and investigation of heterogeneity

*See:* [MECIR C22](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/planning-review-methods-protocol-stage-c19-c23); [MECIR PR36](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40) [Section 10.11 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-10#section-10-11).

Describe the subgroup analyses you are planning and state for which outcomes they will be computed. Provide brief justifications for the sub-group analyses or refer to any justifications supplied already in the "Background" or "Criteria for considering studies for this review" sections. Ensure that you describe the different subgroups clearly, so that it is clear what groups are being compared.

In general, subgroup comparisons will not provide meaningful information in analysis if the number of studies available for meta-analysis of the outcomes is limited. While there is no hard and fast rule, if fewer than 10 studies are available, it is unlikely that subgroup comparisons will offer meaningful, interpretable results. A test for interaction is needed to evaluate whether the pooled estimates for each subgroup of studies truly differ. The statistical significance of a pooled estimate from a subgroup of studies should not be interpreted as evidence of a subgroup difference.

**Suggested language:**

*Tests for subgroup differences in effects will be interpreted with caution given the potential for confounding with other study characteristics and the observational nature of the comparisons.* *See* [Section 10.11.2 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-10#section-10-11-2). *In particular, subgroup analyses with fewer than five studies per category are unlikely to be adequate to ascertain valid difference in effects and will not be highlighted in our results. Subgroup comparisons will not be undertaken when there are fewer than ten studies available for meta-analysis. When subgroup comparisons are possible, stratified meta-analysis and a formal statistical test for interaction will be conducted to examine subgroup differenc*e*s that could account for effect heterogeneity (e.g., Cochran’s Q test, meta-regression) (Higgins 2020b; Borenstein 2013).*

*Given the potential differences in the intervention effectiveness related to [….] discussed in the Background section, we will conduct subgroup comparisons to see if the intervention is more effective for […].*

*We plan to carry out the following subgroup analyses of factors that may contribute to heterogeneity in the effects of the intervention: [Be specific, limit comparisons to a few variables that may contribute to heterogeneity in effects]*

1. *E.g. Studies limited to nulliparous participants versus studies enrolling nullipara and multipara*
2. *E.g. Studies using intervention dosage <100mg versus studies >100mg*

*We will use the following outcomes in subgroup analyses if there are enough studies reporting to support valid subgroup comparisons (at least 5 studies per subgroup).*

* 1. *Outcome 1*
  2. *Outcome 2*
  3. *Outcome 3*

*See* [Section 10.11 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-10#section-10-11)

### Sensitivity analysis

In this section describe a small number of planned sensitivity analyses and the reasons for them. Sensitivity analyses can be set to test whether key methodological factors or decisions that may have affected the main results of the review.

Common sensitivity analyses to consider:

*Risk of Bias*: We will compare intervention effects in analyses limited to RCTs…

ROB1: at low risk of bias versus those at high or unclear risk of bias (overall risk of bias).

ROB2 and NRSI: at low risk of bias versus those identified as having some concerns or greater than low risk of bias (overall risk of bias).

*Missing data:* We will conduct sensitivity analyses evaluating the implications on the results that would arise from different assumptions related to missing data.

*Participants*: We will limit the analysis to RCTS that include only participants that met the age range criteria of the review compared to RCTs that included some younger or some older participants.

*Study setting*: Studies conducted in High/Very High Human Development Index settings versus Medium/Low

*Publications statu*s: RCTs published as abstract only and RCTs published in full.

*Analytic technique for meta-analysis*: If you had planned to conduct a fixed-effects meta-analysis but found substantial heterogeneity, you may wish to carry out a sensitivity analysis that compares results from a random-effects model with those from the planned fixed-effects model. Alternatively, if a random-effects model was the default but features of the evidence may warrant the fixed-effects approach a sensitivity analysis with the fixed-effect estimate may be considered.

*See:* [MECIR C71](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/performing-review-c24-c75/synthesizing-results-included-studies-c61-c73); [MECIR R94](https://community.cochrane.org/mecir-manual/standards-reporting-new-cochrane-intervention-reviews-r1-r109/results-r56-r109/effects-interventions-r76-r99); [Section 10.14 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-10#section-10-14).

**Suggested language:**

*[Describe the sensitivity analyses to be conducted based on the list above and the specific issues likely to be of concern for the topic.]*

*Given that there is no formal statistical test that can be used for sensitivity analysis, we will provide informal comparisons between the different ways of estimating the effect under different assumptions. Changes in the p-values should not be used to judge whether there is a difference between the main analysis and sensitivity analysis, since statistical significance may be lost with fewer studies included.*

*We will report sensitivity analysis results in tables rather than forest plots.*

### Summary of findings and assessment of the certainty of evidence

This section describes your plan for synthesis of your summary of findings table. The table can include up to seven (pre-specified) outcomes, including primary/critical outcomes, adverse events and all patient important outcomes or those that are most important to guideline setters and people making decisions about healthcare.

**Suggested language:**

*We will evaluate the evidence on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes.*

*We will follow the methods and recommendations described in* [Chapter 14](https://training.cochrane.org/handbook/current/chapter-14) of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2020](about:blankSchünemann%202019)) *and the use of GRADEpro software* ([GRADEpro GDT 2015](about:blankGRADEpro%20GDT%202015)).

*A separate Summary of Findings table will be provided for each of the following comparisons to be evaluated in this review:*

*LIST COMPARISONS*

*Decisions to downgrade the certainty of studies will be justified using footnotes and comments will be provided to aid reader's understanding of the review where necessary.*

*Judgements about the evidence certainty will be made by two review authors (add authors initials) working independently, with disagreements resolved by discussion or involving a third author (initials). Judgements will be justified, documented and incorporated into reporting of results for each outcome.*

See [MECIR C23](https://community.cochrane.org/mecir-manual/standards-conduct-new-cochrane-intervention-reviews-c1-c75/developing-protocol-review-c1-c23/planning-review-methods-protocol-stage-c19-c23); [MECIR PR39-PR40](https://community.cochrane.org/mecir-manual/standards-reporting-protocols-new-cochrane-intervention-reviews-pr1-pr44/reporting-review-plan-pr1-pr44/data-collection-and-analysis-pr22-pr40); [Chapter 14 Cochrane handbook version six](https://training.cochrane.org/handbook/current/chapter-14).

**RESOURCES**

**REFERENCES**

***Borenstein 2013***

*Borenstein M, Higgins JPT. Meta-Analysis and Subgroups. Prev Sci 14, 134–143 (2013).* [*https://doi.org/10.1007/s11121-013-0377-7*](https://doi.org/10.1007/s11121-013-0377-7)

***Campbell 2019***

*Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. BMJ 2020;368:l6890* [*http://dx.doi.org/10.1136/bmj.l6890*](http://dx.doi.org/10.1136/bmj.l6890)

***Cohen 1988***

*Cohen J. Statistical Power Analysis in the Behavioral Sciences. 2nd edition ed. Hillsdale (NJ): Lawrence Erlbaum Associates, Inc.; 1988*

***Deeks 2020***

*Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from* [*www.training.cochrane.org/handbook*](http://www.training.cochrane.org/handbook)

***Egger 1997***

*Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634*

***EPOC 2013***

Cochrane Effective Practice and Organisation of Care (EPOC). EPOC worksheets for preparing a 'Summary of findings' table using GRADE. EPOC resources for review authors. Available from epoc.cochrane.org/epoc-specific-resources-review-authors 2013.

***GRADEpro GDT 2015***

GRADEpro GDT [Computer program]. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

***Guyatt 2008***

Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-6.

***Higgins 2011***

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

***Higgins 2020a***

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions*version 6.1 (updated September 2020). Cochrane, 2020. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

***Higgins 2020b***

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

***Liberati 2009***

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Medicine 2009;6(7):e1000100. Higgins 2019

***McKenzie 2020***

*McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from* [*www.training.cochrane.org/handbook*](http://www.training.cochrane.org/handbook)

***Schünemann 2020***

*Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, Guyatt GH. Chapter 14: Completing ‘Summary of findings’ tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from* [*www.training.cochrane.org/handbook*](http://www.training.cochrane.org/handbook)

***Sterne 2011***

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002 [DOI: 10.1136/bmj.d4002]

***Sterne 2016***

Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919

***Sterne 2019***

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; **366**: l4898.