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Template for Intervention review

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Abstract

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

See MECIR Protocol Standards – Objectives (PR5-PR8)

To assess the [effects/benefits/harms] of [intervention] compared with [comparison(s)] for [health problem] in [population, disease, setting, etc].

Background

Introduction text for authors *(please delete before submission for editorial approval)*

This protocol template is designed for new protocols of intervention reviews. It includes template suggested text addressing all mandatory Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards (see here) ensuring consistency across PaPaS reviews.

We recognise some text may need to be adapted according to the scope of the review and so authors are free to amend it ensuring **all expected standardsare met**.

Timelines

First draft protocols should be submitted for editorial approval **within six months** of title registration; if this deadline is not met the title will be automatically de-registered unless there are extenuating circumstances. We expect to publish the protocol within 12 months of registration. PaPaS reserves the right to withdraw titles that greatly exceed the submission deadlines, or fail to meet the minimum standards. **Please keep in touch with us regarding the progress of your protocol. The team is always happy to discuss any issues arising at any stage.**

Some useful links

- Cochrane Handbook versions 2020 (and 2011 for Risk of bias 1.0)
- The Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards for the conduct and reporting of Cochrane protocols (also available for full reviews).
- Cochrane Training interactive learning modules and guidance
- PaPaS step-by-step editorial process for protocols
- PaPaS contact details

Before submitting your draft for editorial approval (see Quick Start Guide for Authors), it is recommended that you:

- run a spell check;
- ensure the protocol is written in active voice;
- check that all sources have been referenced;
- check that your text and references adhere to the Cochrane Style Basics;
- check there are no 'Errors' and review the 'Warnings' on the Validation Report (RevMan 5: File > Reports > Validation Report; in RevMan Web, this is visible on the Dashboard);
- check review author initials have been added for key review tasks such as sifting references, data extraction, risk of bias, data analysis and GRADE;
- delete all guidance text.

Background guidance

See MECIR Protocol Standards – Background (PR3-PR4)*. Authors may also want to consider* Chapter 16: Equity and specific populations *(Cochrane Handbook 2019) when preparing the 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. See Section III.3.2 of the Cochrane Handbook for Systematic Reviews of Interventions.

There may be a recent PaPaS reviewthat could be used as a template for this section for consistency in the Library (e.g. neuropathic pain, migraine).

Description of the intervention

Describe the intervention(s), placing it in the context of any standard, alternative and comparator interventions, and noting whether standard practice varies by context or geographical location. If the intervention is a drug, include basic information on clinical pharmacology such as dose range, metabolism, selective effects, half-life, duration of the intervention and any known interactions with other drugs. For complex interventions such as behavioural or service-level interventions, provide a description of the main components (see Chapter 17 of the Cochrane Handbook for Systematic Reviews of Interventions). See Section III.3.2 of the Cochrane Handbook for Systematic Reviews of Interventions.

There may be a recent PaPaS reviewthat could be used as a template for this section for consistency in the Library (e.g. antidepressants, exercise).

How the intervention might work

It is highly desirable to include any details of equity and howthe intervention relates to specific populations if this is relevant. See MECIR C4 and Section 2.4.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

Why it is important to do this review

Refer, among other points, to national and international guidelines in this section. See MECIR PR3-PR4; Chapter III and Section III.3.2 of the Cochrane Handbook for Systematic Reviews of Interventions.

Add if relevant: This protocol replaces the original version and will serve to update it [add ref].

Objectives

See MECIR Protocol Standards – Objectives (PR5-PR8)

To assess the [effects/benefits/harms] of [intervention] compared with [comparison(s)] for [health problem] in [population, disease, setting, etc].

Methods

Criteria for considering studies for this review

Types of studies

We will include [randomised controlled trials (RCTs) with double-blind assessment of participant outcomes]. *[Provide explicit justification of the choice of study design(s), e.g. Randomised trials are the best design to minimize bias when evaluating the effectiveness of an intervention.]*

We will include online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts; if there are insufficient data for analysis in the abstracts, we will attempt to locate the full study (e.g. by contacting the study authors). If the data from the full study are unavailable, we will add the abstract to 'Studies awaiting classification'.

We will exclude non-randomised studies, experimental studies using pain induction, case reports and clinical observations.

*Also state explicitly whether crossover, cluster RCTs or quasi-RCTs will be eligible and justify the decisions. Parallel and crossover trials are randomised at the level of the participant, and cluster RCTs are randomised at the cluster level. Quasi-RCTs are parallel-arm RCTs in which allocation is decided by an approximation of randomisation (e.g. allocation by patient ID number), and can be assessed for bias using the RoB 2 tool (*Sterne 2019*). Studies where allocation includes features related to prognosis or disease progression may need to be assessed using the ROBINS-I tool, which is designed to assess issues-related confounding.*

See MECIR C9*;* MECIR PR9-PR10*;* Chapter 2 *and* Section 2.3 *of the Cochrane Handbook for Systematic Reviews of Interventions.*

Types of participants

We will include studies of *[adults]* aged *[18 years and above] [plus setting, diagnosis or definition of condition and demographic factors where relevant]*. We will address studies including subsets of relevant participants by *[state your methods here; see* Handbook Chapter 3*]*.

Special populations of interest are *[list, e.g. adults over 75; those with pre-existing health conditions)]*

We will exclude studies of [*list ineligible populations*].

Define in advance how you will handle studies that include only a subset of relevant participants (e.g. contact study authors to obtain data, include if more than X% of participants are eligible). Justify and describe restrictions to study populations here. Define an age cut-off for adults/children/infants. See MECIR C5-6*;* MECIR PR11*;* Section 3.2 *of the Cochrane Handbook for Systematic Reviews of Interventions.*

Types of interventions

[Intervention] *[delivery, dose, duration, intensity, co-interventions]*, administered for *[condition]* and compared to *[comparison(s)]*.

*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 type of therapy). If more than one comparison is planned, define each one, preferably as a list (e.g. statin versus placebo; warfarin plus aspirin versus warfarin). Where relevant, state how you will manage cointerventions (*Section 3.2.3.1 *of the Cochrane Handbook for Systematic Reviews of Interventions). Indicate any specific aspects related to the intervention or comparator (e.g. route of administration, duration of intervention and frequency) and reflect these in the* Data collection and analysis *section. For multi-component or*

complex interventions, define any common or core features that will define that intervention. State that you will list all treatment arms of each study in the 'Characteristics of included studies' table (this is a requirement in MECIR C50). See MECIR C7; MECIR PR12; Section 3.2.2 of the Cochrane Handbook for Systematic Reviews of Interventions.

Types of outcome measures

Specification of outcomes should include consideration of outcome domains (e.g. quality of life) and specific measures (e.g. 36-item Short Form (SF-36)), and which time points are important. The level of detail that you list about outcomes will reduce the risk of selective outcome reporting and potential biases in the review process and may affect your RoB 2 assessments.

Critical outcomes should be as few as possible and should normally reflect at least one potential benefit and at least one potential harm. It is expected that the review should be able to synthesise these outcomes if eligible studies are identified, and that the conclusions of the review will be based largely on the effects of the interventions on these outcomes. Additional important outcomes may also be specified and up to seven outcomes will form the basis of the GRADE assessment, 'Abstract' and 'Plain language summary'.

It is preferable to avoid composite outcomes (such as major adverse events) that may double count participants who had more than one event. The most important types of event should be reflected as separate outcomes.

Reporting one or more of the outcomes listed here in the trial should not be used as an inclusion criterion for the review (MECIR C40). 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 that measured these outcomes but did not report the data, or did not report the data in a usable format will be included in the review as part of the narrative.

See MECIR C8; MECIR C14-C18; MECIR C40; MECIR PR13-PR16; Section 3.2.4 and Section 8.7 of the Cochrane Handbook for Systematic Reviews of Interventions.

Primary outcomes

State your primary/critical outcomes in detail as described above in order of importance.

Secondary outcomes

State your secondary/important outcomes in detail as described above in order of importance.

Search methods for identification of studies

See MECIR Protocol Standards – Search methods for identifications of studies (PR17-PR21); MECIR C19; Section 4.5 of the Cochrane Handbook for Systematic Reviews of Interventions.

Electronic searches

We will search the following databases without language restrictions. *[Note: where relevant we can seek translational assistance]*

- The Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library) (latest issue)
- MEDLINE (via Ovid)
- Embase (via Ovid)
- *[Add others as required]*

We will tailor searches to individual databases. The search strategy for MEDLINE is in Appendix 1.

The search strategy will be developed by the PaPaS Review Group's Information Specialist and will be independently peer reviewed. The PaPaS Information Specialist will perform the searches. *[Can be amended where author teams have access to their own IS.]*

Searching other resources

We will search clinicaltrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials. In addition, we will search grey literature, check reference lists of reviews and retrieved articles for additional studies, and perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors for additional information where necessary.

Data collection and analysis

Selection of studies

Two review authors *[initials, if known]* will independently determine eligibility of each study identified by the search. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and will obtain full copies of the remaining studies. Two review authors *[initials]* will read these studies independently to select relevant studies, and in the event of disagreement, a third author will adjudicate *[initials]*. We will not anonymise the studies in any way before assessment. We will include a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart in the full review (Liberati 2009). We will include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.

See MECIR C39-C42*;* MECIR PR22 to PR26*;* Section 4.6 *of the Cochrane Handbook for Systematic Reviews of Interventions.*

Data extraction and management

Two review authors *[initials if known]* will independently extract data using a standard piloted form and check for agreement before entry into Review Manager *[RevMan 5.4 or RMW (add ref)]*. In the event of disagreement, a third author will adjudicate *[initials]*. 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 collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review.

We will extract the following information. *[Authors free to add/amend accordingly, in line with Cochrane standards]*

- Methods: study design, total duration of study, details of any 'run-in' period (if applicable), number of study centres and location, study setting, and date of study.

- Participants: number randomised, number lost to follow-up/withdrawn, number analysed, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria (add any other characteristics that you will extract).
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: outcomes specified and collected, and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.Information needed to assess bias (e.g. any deviations from intended interventions, were data imputed for key outcomes, etc.).
- Information needed to assess GRADE (e.g. baseline risk in the control group for key outcomes).

See MECIR C43-C51*;* MECIR PR22 to PR26*;* Chapter 5 *of the Cochrane Handbook for Systematic Reviews of Interventions.*

Assessment of risk of bias in included studies

Risk of bias 1*: PaPaS policy is to use the Risk of Bias (RoB) tool version 1 and so the suggested text belowreflects that. Authors are encouraged to check they agree and understand this approach.*

- *Note that this suggested text is relevant to an intervention reviewof RCTs of pharmacological studies; the wording may need to be adapted for other review types.*
- *If making changes here, please followthe same formatting and provide as much detail as possible, e.g. include justification for low, unclear, and high risk judgements.*
- *Authors are free to move a lot of the detail in this section to an Appendix if preferred.*
- *Authors are free to use RoB 2 if they wish (see below).*

Two authors *[initialsif known]* will independently assess risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), with any disagreements resolved by discussion. We will complete a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager *[RevMan 5.4 or RMW ref]*.

We will assess the following biases for each included study.

- Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as:
    - low risk of bias (any truly random process, e.g. random number table; computer random number generator);
    - unclear risk of bias (insufficient detail about the method of randomisation to be able to judge the generation as 'low' or 'high' risk of bias);
    - we will exclude studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- unclear risk of bias (insufficient detail about the method of randomisation to be able to judge the generation as 'low' or 'high' risk of bias);
- we will exclude studies that do not conceal allocation (e.g. open list).

- ***Blinding of participants and personnel (checking for possible performance bias). We will assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess methods as:
  - low risk of bias (study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique);
  - unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved);
  - we consider studies that were not double-blind to have high risk of bias.
- ***Blinding of outcome assessment (checking for possible detection bias). We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as:
  - low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved);
  - unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks a clear statement on how it was achieved);
  - ***[Authors to check this wording]*** we will [exclude studies / consider studies at high risk of bias] where outcome assessment was not blinded.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as:
  - low risk (no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; missing data have been imputed using 'baseline observation carried forward' analysis);
  - unclear risk of bias (insufficient reporting of attrition/exclusions to permit a judgement of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided, or the study did not address this outcome));
  - high risk of bias (reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation).
- Selective reporting (checking for reporting bias). We will assess reporting biases due to selective outcome reporting. We will judge studies as:
  - low risk of bias (the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the

review have been reported in the prespecified way);

- unclear risk of bias (insufficient information available to permit a judgement of 'low risk' or 'high risk');
- high risk of bias (not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes have been reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review have been reported incompletely so that they cannot be entered in a meta-analysis; the study report failed to include results for a key outcome that would be expected to have been reported for such a study).

*[***There are circumstances where blinding of participants and personnel may not always be possible (for example, surgery, psychological interventions, pharmacological interventions for cancer pain). There may also be reasons why blinding of outcome assessors is not possible. In this circumstance give the reason(s) why blinding is not possible. The potential for bias may be dependent on outcome as well, with greater potential bias for subjective than objective outcomes.*

It is possible to separate outcome and study level biases in the risk of bias table properties in RevMan. For blinding and incomplete outcome data, for example, you can judge risk of bias separately for subjective and objective outcomes (e.g. pain and mortality). See 2011 Handbook Chapter 8*.*

There might also be double-blind studies where efforts to maintain blinding of participants have failed, because adverse events which unmask treatment group assignment for example. Such studies should still be included in the review.]

Risk of bias 2*: If using RoB 2, the following information should be described in the protocol (see* Chapter 8 *of the Cochrane Handbook for Systematic Reviews of Interventions for more information and* Risk of Bias 2 (RoB 2) tool*).*

- *State the name of the tool and the domains that will be assessed (1. bias arising from the randomisation process; 2. bias due to deviations from intended interventions; 3. bias due to missing outcome data; 4. bias in measurement of the outcome; and 5. bias in selection of the reported result).*
- *State the relevant variations of the tool that will be used for cluster and cross-over RCTs, if included.*
- *State 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 protocol (the 'per-protocol effect') (*Hernán 2017 *(Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. New England Journal of Medicine 2017;377:1391-8)).*
- *State that signalling questions in the RoB 2 tool will be used to rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias' (*Sterne 2019 *(Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I,. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898)).*

- *State that risk of bias judgements will be summarised for each outcome across different studies for each of the domains listed, where the overall risk of bias for the result is the least favourable assessment across the domains of bias.*
- *State whether answers to signalling questions (e.g. using the Excel tool available on www.riskofbias.info) will be made available online (e.g. on data repository websites such as figshare).*
- *State which specific named results will be assessed (e.g. those included in the 'Summary of findings' table(s)). Outcomes, measures and timings should be included in 'Summary of findings' table(s) and should be prespecified by review authors.*
- *Prespecify how risk of bias will be used to inform the review (taking assessments into account for specific treatment effects; whether the primary analysis will be limited to studies at overall low risk of bias; if you will be performing sensitivity analyses or subgroup analyses (and on what basis).*
- *State that figures will be included to illustrate risk of bias and that where possible you will add this information to figures showing meta-analysis.*
- *State that risk of bias assessment will inform GRADE and the 'Summary of findings' table(s).*

For Domain 2 list potential 'non-protocol interventions'. See Section 8.4 of the Cochrane Handbook for Systematic Reviews of Interventions.

For Domain 5, bias in the selection of the reported result, note that the amount of specific detail you provide about your outcomes of interest in the 'Types of outcomes' section of the protocol can affect the level of bias in RoB 2.

RoB 2: assessment of risk of bias in cluster-randomised trials and cross-over trials

The Cochrane RoB 2 tool has variations of the tool drafted to assess specific issues of potential bias related to these study designs (see Section 23.1.2 and Section 23.2.3 of the Cochrane Handbook for Systematic Reviews of Interventions).

Some of the signalling questions and guidance for RoB 2 for cluster-RCTs differ to those for parallel RCTs (considerations for missing data and baseline imbalances) and the cluster variant of the tool includes one additional domain.

- *Bias arising from the timing and recruitment of participants.*

RoB 2 for cross-over RCTs is very similar to the tool for parallel RCTs but some of the signalling questions and guidance differ from those for parallel RCTs and the cross-over variant of the tool includes one additional domain.

- *Bias arising period and carryover effects.*

See MECIR C20; MECIR C52-C60; MECIR PR27-PR28; Chapter 7 and Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.

Measures of treatment effect

State your choice of treatment effect to analyse. State 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). For example, "We will analyse

dichotomous data as risk ratios (or odds ratios, if this is your preference) with 95% confidence intervals (CI) and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CIs. We will enter data presented as a scale with a consistent direction of effect".

Explain circumstances where you would use SMD and where you would use MD, and how you plan to interpret SMD analyses (SMDs are used when different scales are used to measure an outcome, thus necessitating the standardisation of the results of the studies to a uniform scale before they can be combined, see Section 15.5 *of the* Cochrane Handbook for Systematic Reviews of Interventions *for more guidance).*

State that, if data are not reported in an RCT in a format that you can enter directly into a meta-analysis, that you will convert them to the required format using the information in Chapter 6 *of the* Cochrane Handbook for Systematic Reviews of Interventions.

If you are using a threshold to represent a clinically important or smallest worthwhile effect please define and justify it here.

See MECIR C21; MECIR C47; MECIR C61; MECIR PR29; Chapter 6 *of the* Cochrane Handbook for Systematic Reviews of Interventions.

Unit of analysis issues

State what approach you will take for RCTs with three or more arms or for RCTs with repeated outcome measurement at different time points (or, where relevant, for RCTs where the comparison is between parts of the body, e.g. data from left and right side of the mouth, data from left eye and right eye, etc.). Consider methods that will avoid double-counting in the meta-analysis. For RCTs with parallel design and only two arms (intervention 1 versus control or intervention 1 versus intervention 2), you do not need to consider unit of analysis issues, but you may encounter studies with three or more intervention arms of interest. Describe how cluster RCTs or crossover RCTs will be analysed.

See MECIR PR30; MECIR C70; Section 6.2, Section 23.1 *and* Section 23.1.2 *of the* Cochrane Handbook for Systematic Reviews of Interventions.

Dealing with missing data

State the methods you will use to identify additional and unpublished data (e.g. contacting investigators or study sponsors to verify key study characteristics or obtain missing outcome data).

State (or if you have described this under 'Measures of treatment effect' refer to that section) that you will calculate missing standard deviations or other necessary data using other data from the trial, such as CIs, based on methods outlined in Chapter 6 *of the* Cochrane Handbook for Systematic Reviews of Interventions *(*Higgins 2020b*).*

State how you will work to reduce bias from missing data by conducting sensitivity analyses (see MECIR C64*). Several approaches for assessing risk of bias due to missing results are outlined in* Chapter 13 *of the* Cochrane Handbook for Systematic Reviews of Interventions. *A thorough assessment of selective non-reporting or under-reporting of results in the studies identified is likely to be the most valuable. The number of identified studies that have results missing for a given synthesis is known, and so the impact of selective non-reporting or under-reporting of results can be quantified more easily than the impact of selective non-publication of an unknown number of studies.*

See MECIR C47*;* MECIR C64*;* MECIR PR26*;* Section 6.3 *and* Chapter 13*of the* Cochrane Handbook for Systematic Reviews of Interventions.

Assessment of heterogeneity

State how different types of heterogeneity will be investigated, including clinical diversity (participants, interventions, etc. within the RCTs), methodological diversity (study design, outcome measurement tools used, etc.), and statistical heterogeneity (variability in the numerical effect estimates resulting from clinical and methodological diversity). State how key clinical and methodological characteristics and effect modifiers will be summarised for the included studies to inform your discussion and conclusions. Data for clinical and methodological variability are usually covered in the 'Characteristics of included studies' table. It can be helpful to provide an easily viewed overview of these in stand-alone tables.

State how you plan to assess statistical heterogeneity by visual inspection of forest plots to consider the direction and magnitude of effects and the degree of overlap between CIs.

Define which statistics will be used to assess heterogeneity (e.g. "We will use the I^2 statistic to quantify inconsistency among the trials in each analysis. We will also consider the P value from the Chi^2 test. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis." Indicate the uncertainty around measures such as the I^2 statistic *and Tau when there are few studies and avoid using simple thresholds to interpret statistical heterogeneity.*

Presenting an approximate guide to interpretation may be useful (e.g. Deeks 2020*):*

- *0% to 40%: 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 the I^2 statistic depends on 1. magnitude and direction of effects, and 2. strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small).

A full description of means to assess heterogeneity is covered in Section 10.10*of the* Cochrane Handbook for Systematic Reviews of Interventions.

See MECIR C62*;* MECIR C63*;*MECIR PR32*;*Section 10.10 *of the* Cochrane Handbook for Systematic Reviews of Interventions*.*

Assessment of reporting biases

State whether funnel plots will be used, for which outcomes and whether a formal statistical test for asymmetry will be used (e.g. Egger 1997*). These are recommended if you have sufficient studies (approximately 10) included in your meta-analyses. Funnel plots are not advised for meta-analyses of fewer than 10 studies because the ability to detect publication bias will be largely diminished.*

Funnel plot asymmetry may arise because of small-study effects and not just non-reporting bias.

Consult a statistician and Sections 13.3.5.2 to 13.3.5.4 *of the* Cochrane Handbook for Systematic Reviews of Interventions *if you intend to explore possible non-reporting*

bias.

Refer to Chapter 13*on missing results in a synthesis of the* Cochrane Handbook for Systematic Reviews of Interventions.

See MECIR C73; MECIR PR34; Chapter 13*of the* Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis

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

Meta-analysis of numerical data

State whether you plan to use a random-effects or a fixed-effect model and justify your choice. 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*of the* Cochrane Handbook for Systematic Reviews of Interventions 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 the* I^2 statistic.

Synthesis using other methods

Prespecify the approach that will be taken to present outcome data if it is not possible to pool numerical data in a meta-analysis for one or more outcomes. See Table 12.1.a*of the* Cochrane Handbook for Systematic Reviews of Interventions.

Present a hierarchy of approaches to be taken depending upon the amount of data found. A range of appropriate methods are available in Chapter 12 Cochrane handbook version six that contains many useful methods that are aimed at reducing bias in presentation of synthesis using other methods or SWiM. A statement that you plan to follow guidance in Chapter 12 *would be sufficient but add more detail if you wish. Vote counting based on statistical significance is not an appropriate method.*

See MECIR C21; MECIR PR33; Chapter 12*of the* Cochrane Handbook for Systematic Reviews of Interventions; Webinar 1 on SWiM.

Subgroup analysis and investigation of heterogeneity

Clearly describe any planned subgroup analyses making it clear which groups will be compared and for which outcomes. Clearly outline how subgroups for each analysis will be defined. Include brief justifications (referring to the 'Background' or 'Criteria for considering studies for this review' sections if appropriate).

To make a valid investigation of subgroup differences, state use of a formal test to assess for subgroup differences. See Section 10.11*of the* Cochrane Handbook for Systematic Reviews of Interventions.

State awareness of the limitations of subgroup analyses that require consideration when interpreting results, including their observational nature (*see* Section 10.11.2*of the* Cochrane Handbook for Systematic Reviews of Interventions) and power to detect differences *with fewer than 10 studies per category.*

Consult the Cochrane Handbook for Systematic Reviews of Interventions *or a statistician if you plan to assess heterogeneity using meta-regression, and state all methods clearly (*Higgins 2020a*).*

See MECIR C22*;*MECIR PR36*;*Section 10.11*of the* Cochrane Handbook for Systematic Reviews of Interventions.

Authors may wish to include the following template text.

We plan to carry out the following subgroup analyses where there is significant heterogeneity:

1. add
2. add
3. add

We plan to include the following outcomes (usually primary) in subgroup analyes:

1. add
2. add
3. add

We will perform the formal test for subgroup interactions in Review Manager.

Sensitivity analysis

State any planned sensitivity analyses and the reasons for them (e.g. to test whether key methodological factors or decisions have affected the main result; see Section 10.14*of the* Cochrane Handbook for Systematic Reviews of Interventions).

Examples include: characteristics of bias (see below) (e.g. RCTs that are at high risk of bias compared to those at low risk of bias, or some concerns); characteristics of participants (e.g. participants in some RCTs meet the age range criteria of the review and in other RCTs include some younger or some older participants); characteristics of publications status (e.g. RCTs published as abstract only and RCTs published in full); characteristic of the outcome (e.g. time point of assessment or means of measurement); characteristics of the comparator (e.g. variations in what is considered treatment as usual, or control).

If you plan to consider risk of bias in a sensitivity analysis, then for RoB 2, using overall risk of bias is recommended (low risk, some concerns or high risk) rather than bias determined for individual domains. Primary analyses can be restricted to studies judged at an overall low risk of bias or low risk of bias and some concerns. Unlike subgroup analysis, there is no formal statistical test that can be used for sensitivity analysis, so review authors must make informal comparisons between the different ways of estimating the effect under different assumptions. Comparing changes in P values to judge whether there is a difference between the main analysis and sensitivity analysis is not appropriate.

See MECIR C71*;*MECIR R94*;*Section 10.14*of the* Cochrane Handbook for Systematic Reviews of Interventions.

Summary of findings and assessment of the certainty of the evidence

If using RevMan 5 (desktop) and not RevMan Web, this subheading will need to be added manually using Heading Style 3.

Two review authors (*initials if known*) will independently rate the certainty of the body of evidence for the outcomes, with disagreements resolved by discussion or involving a third review author (*initials)*. We will justify, document and incorporate judgements into reporting of results for each outcome. We will use the GRADE system to rank the certainty of the evidence using [the GRADEprofiler Guideline Development Tool software (GRADEpro GDT)/other - add ref], and the guidelines provided in the *CochraneHandbook for Systematic Reviews of Interventions* (Schünemann 2020).

The GRADE approach uses five considerations (study limitations (risk of bias), unexplained heterogeneity and inconsistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

The GRADE system considers study design as a marker of quality. Randomised controlled trials are considered to be high quality of evidence and can be downgraded for important limitations.

Factors that may decrease the certainty level of a body of evidence are as follows.

- Serious or very serious study limitations (risk of bias)
- Important or serious inconsistency of results
- Some or major indirectness of evidence
- Serious or very serious imprecision
- Probability of publication bias

We plan to include *[n]* summary of findings table(s) to present the main findings for *[comparison(s)]* in a transparent and simple tabular format. In particular, we will include key information concerning the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes [*list up to seven*].

Please include at least one template SoF table (see example added in summary of findings table section below); this will not be published and can be amended later, but is a useful tool to consider the optimum structure a priori.

Acknowledgements

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expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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The Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) supported the authors in the development of this review.

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Describe the contribution of each review author in the protocol.

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Example text, for the protocol of a review on pharmacological interventions for neuropathic pain:

AA: none known.
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CC: none known; CC is a specialist chronic pain physician and manages patients with neuropathic pain.
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- No sources of support provided

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Appendices

Appendix 1. Add your search strategy here

Check link to Appendix 1 in Electronic searches.

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