A practical guide:

Protocol Development for Systematic Reviews

covidence

Introduction

Welcome to this practical guide to protocol development for systematic reviews. Whether you're an experienced researcher or just starting out, this guide can help you develop your review protocol which will help you plan and manage your systematic review.

Inspired by the knowledge of hundreds of researchers, this guide compiles best practices and tips from the global systematic review community. It features clear definitions, practical advice, a downloadable template, and real-world study examples.

We hope this guide becomes an essential part of your research journey.

About the author

We are Covidence. Launched in 2014, Covidence is a not-for-profit world leading Software as a Service (SaaS) platform. Our platform enables health and science research teams to rapidly synthesise and uncover actionable insights from the mountains of research produced around the world. Leading institutions worldwide use Covidence to create the knowledge that shapes our society.

If you find this guide helpful, please share it with your community so everyone can benefit. Feel free to use the pictures and drawings in your own content. We'd appreciate it if you could include a shout-out: 'Diagrams and illustrations courtesy of Covidence,' along with a hyperlink to the eBook whenever you can. Thanks for spreading the word!

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01

Introduction

Why is it important to write a protocol?

A systematic review protocol is key to ensuring the integrity, transparency, and rigour of the systematic review process - leading to more reliable and credible research outcomes. The review protocol should be written by the review team which should, where possible, include both subject-matter experts and experienced reviewers.

Review team   →   Review protocol

The systematic review protocol is important for the following reasons:

- **Efficiency:** A protocol streamlines the review process by providing structured guidance on each section of the review. Structure enables the reader to quickly identify a relevant section of the protocol. A protocol can also be used to create the data extraction template and form the basis of the final systematic review report, ultimately saving the review team time.

- **Planning:** Planning can save time and resources. Planning provides a roadmap for the review process. It can be used to identify tasks for team members, keep the team on track and aligned during tasks, and avoid introducing biases. It can act as a quality assurance tool, allowing feedback prior to embarking on the full review and may increase the chance of publication, especially if the protocol has been registered. The protocol can be a useful planning tool for higher-degree students and their supervisors and as a piloting tool for search strategies and data extraction templates.

- **Transparency and reproducibility:** A protocol provides a transparent outline of the planned methods and procedures for the systematic review before it is conducted. It can highlight issues around potential selective reporting. The protocol allows others to replicate the study and promotes confidence in the results and conclusions of the review.

- **Minimising bias and ensuring accountability:** Pre-specifying criteria for study selection, data extraction, and analysis can reduce the risk of introducing bias into a systematic review. Comparing the protocol with the completed review can detect unintentional or undocumented changes. Selective reporting, or not reporting, of outcomes based on direction of treatment effect or statistical significance results in bias. The review team should be accountable and justify any deviation from the protocol.

- **Reducing errors and discrepancies:** Planning and pre-specifying methods can help reduce errors and discrepancies during the review process. Clearly defined criteria and procedures minimise the chance of mistakes, prevent arbitrary decision-making and ensure consistency in the approach to study selection and data extraction.

- **Prevents research waste:** In a time when there is increasing awareness of research wastage, the development and registration or publication of a systematic review protocol, where appropriate, may reduce duplication of effort. This can be important to higher degree students to indicate that their area of research is under investigation.

💡 Tips on writing style for a protocol

- **Tense** - Always write a systematic review protocol in the **future tense** "Two reviewers will independently screen titles and abstracts" rather than the past tense "Two reviewers screened titles and abstracts".

- **Voice** - Use the **active voice** "we will screen…" rather than the passive voice "the titles and abstracts will be screened".

- **Language** - Where possible use **accessible language** as not all readers of systematic reviews are academics or health professionals. Try to avoid technical jargon.

- **Structure**: Write your protocol using **full sentences** and where possible avoid bullet points.

Registering a Protocol

Registering the review protocol is critical to promote transparency, reduce bias and prevent research duplication. The review protocol should detail any plans for submission to a registry. Protocol submission should be prospective.

Review teams may register their review protocols for the following reasons:

- **Transparency and reproducibility:** Transparency allows others to see that this work is in progress. Research questions, objectives, eligibility criteria, and planned analyses are documented. This reduces the risk of bias or selective reporting. Protocol registration also allows other review teams to replicate and evaluate the methodology against best practices. This helps them identify evidence gaps where they can add to the knowledge base. Peer review of protocols submitted to registries can increase the rigour of the review plan ensuring that all steps of the protocol are aligned. Publication of protocols reduces duplication.

- **Minimisation of arbitrary decisions, and maintaining methodological rigour:** Creating and registering the review protocol is a key step in minimising arbitrary decisions. The process of registering the protocol requires careful consideration by the research team on ensuring the research question is well defined and specific and developing the search strategy to identify relevant studies.

- **Reduction of research wastage/duplication:** Protocol registration helps prevent duplication of effort and research wastage. Review teams can confirm that their review has not been done before by checking available registries.

- **Publication and funding requirement:** The prospective registration of a review protocol is often a requirement of some funding agencies and journals, or is strongly recommended.

📘 **The PRISMA Reporting Standard and the Cochrane Handbook**

The PRISMA Reporting Standard and the Cochrane Handbook list completing a protocol as one of the important review steps.

Main protocol registries

Several international networks are available to register systematic reviews:

- PROSPERO**:** the first prospective register of systematic reviews with a focus in healthcare, public health, crime, justice, social welfare, and education. Systematic reviews, rapid reviews, and umbrella reviews can be registered in PROSPERO's database. Scoping reviews are not registered on this platform and students are not able to register their reviews here.

- INPLASY**:** accepts a wider variety of protocols including scoping reviews. Retrospective protocol registration is possible but is strongly discouraged. Protocols are usually published within 48 hours.

- Open Science Framework (OSF)**:** contains pre-published manuscripts and pioneering research protocols. Pre-registration regarding the project is required to capture key information that is permanently stamped with a DOI. Information can be made private for up to four years. Updates can be made throughout this time. A central repository can be created to collaborate with other researchers on the team.

- Research Registry**:** includes all types of research studies including systematic reviews. Allows prospective and retrospective registrations.

Some journals request registration information before journal submissions. Some registries provide a unique registration number that authors can include in their final publications.

Some registries provide a unique registration number /link for a protocol that can then be added to publications and reports.

Cochrane review protocols are automatically registered and uploaded to PROSPERO when they are published.

Campbell Collaboration is another platform that houses a list of registered titles of systematic reviews. These reviews are published once they reach the protocol stage. The Joanna Briggs Institute (JBI) also registers protocols. Protocols that are listed on their site may already be published or in preparation for publication within six months from the initial registration.

Useful resources

Pieper, D., Rombey, T. Where to prospectively register a systematic review. Syst Rev 11, 8 (2022).

📄 Examples

In accordance with best practice, we plan to prospectively register the systematic review protocol with the International Prospective Register of Systematic reviews (PROSPERO).

As this review is an internal project with no anticipated publication, the protocol has not been submitted to a protocol registry.

💡 Tips

Although they cannot register protocols on PROSPERO, students are encouraged to use the platform to aid them in the development of their protocol. This can also be useful for other individuals who have not had experience writing protocols.

If there are any amendments made to a protocol or changes during the review process, the update should also be applied to the registered protocol.
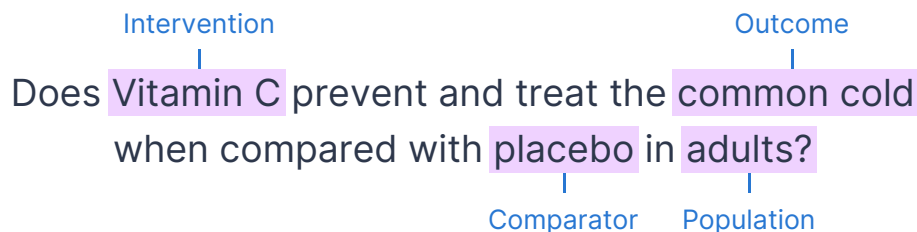
02
Review information

Review Information: Title

The title of a systematic review protocol should provide a concise summary of the study's scope. Structuring titles using the PICO (Population, Intervention, Comparison, Outcome) or PECO (Population, Exposure, Comparison, Outcome) framework can enhance clarity and relevance by systematically organising the key elements of the research question.

Consider including the term "protocol" in the title to indicate that it presents the planned methods and procedures for conducting the review. This helps distinguish it from completed reviews and signals a prospective or ongoing research project.

Consider using the PICO(T) framework to develop your research question for intervention systematic reviews.

Intervention   Outcome

Does **Vitamin C** prevent and treat the **common cold** when compared with **placebo** in **adults?**

                        Comparator   Population

- **Population:** The specific population or group that you want to study. This should include characteristics such as age, gender, medical condition/disease, or any other relevant factors.

- **Intervention:** The treatment, exposure, or intervention you are investigating.

- **Comparison:** The comparison group or alternative intervention you are investigating. This can be a placebo, another treatment, standard care, or the absence of the intervention.

- **Outcomes:** The outcomes you are interested in measuring or evaluating. These can be clinical outcomes, patient-reported outcomes, adverse events, or any relevant endpoints. Consider including outcomes that matter to the end users of the review.

- **Timepoints:** Some reviews include time points as part of the PICO(T) framework. You might be interested in collecting data only at specific timepoints.

- **Other:** Other essential eligibility criteria for your review such as study design.

📑 **Example title**

Title: "Vitamin C versus placebo for the prevention and treatment of the common cold in healthy adults: A protocol for a systematic review and meta-analysis"

Framework: PICO

Explanation: This title clearly identifies the **P**opulation (healthy adults), **I**ntervention (Vitamin C), **C**omparator (placebo), **O**utcome (number of colds), and includes "protocol" to indicate ongoing research.

Review information: Authors/Reviewers

Providing a list of the review team members and their roles is critical to ensure quality, credibility and transparency in systematic reviews. By acknowledging contributions, defining responsibilities, and disclosing conflicts of interest, reviewers sustain high standards of research integrity which feeds into the reproducibility and accountability in the review.

📄 **Example review team**

Reviewer 1
Harry Harper, PhD
Reviewer1@example.com
Covidence University, Melbourne, Australia
Role: Principal Investigator
Responsibilities: Overall project oversight, protocol development, study selection, data extraction, quality assessment, interpretation of results, manuscript preparation.

Reviewer 2
George Grant, MD
Reviewer2@example.com
College of Health, United States
Role: Co-Investigator
Responsibilities: Protocol development, study selection, data extraction, quality assessment, statistical analysis, interpretation of clinical implications, manuscript review.

Reviewer 3
Millie Mills, MPH
Reviewer3@example.com
College of Health, United States
Role: Research Coordinator
Responsibilities: Literature search, study selection, data extraction, quality assessment, data management, coordination of team meetings, protocol adherence.

Reviewer 4
George Good, PhD
Reviewer4@example.com
Covidence University, Melbourne, Australia
Role: Statistician
Responsibilities: Statistical analysis, meta-analysis, assessment of heterogeneity, sensitivity analysis, interpretation of statistical results, manuscript review.

03
Background

Background

The background section, sometimes referred to as the rationale or introduction, of the systematic review protocol should provide **succinct** details on the importance of the review and the reason for conducting it. This section should describe the intervention, how the intervention might work and why it is important to investigate it by identifying the current evidence gaps.

Description of the condition, health issue or problem

Set the scene for your review by providing a brief summary of the aetiology/biology of the condition, health issue or problem that you want to investigate. Detail the prevalence/incidence, diagnostic procedures and prognosis, if relevant. If applicable, report on the impact of the condition on the individual and or community level.

Describe the intervention

It is important to provide detailed information on the intervention/s of interest including components of the intervention (especially in complex interventions), timing/frequency and mode of administration. Explain which population group/s the intervention is intended for and any context in which the intervention is provided. Are there any differences in the use or expected outcomes for different populations (eg, socio-economic group, children, sex).

If the intervention in your review is a drug intervention, you could briefly describe the pharmacology, dosage, metabolism, half-life, drug-drug interactions and any known adverse effects. For a behavioural intervention, describe the component/s of the intervention, detail if the intervention is delivered one-to-one or in a group situation, who delivers the intervention and where it is delivered, frequency and timing of the intervention. Describe any known risks associated with the intervention.

How might the intervention work?

Briefly describe any theoretical or empirical evidence that supports the effect of the intervention. Think about how the intervention might differ from, or supplement, current standard of care or alternate interventions.

Why is it important to do the review?

Provide a brief justification for why you are undertaking this review. Are you looking at the effectiveness of a new intervention? Is your review topic in a newly emerging subject area. Are you comparing one intervention with another? Are you looking to reduce uncertainty or inconsistency in clinical practice? Do you want to investigate patient/consumer choices about an intervention? Provide details on any reviews that already exist that relate to your review topic. Explain why your review differs or supplements current evidence.

04

Review question(s)

Review question and objectives

Getting the review question and objectives right is critical to the whole systematic review process as not all research questions are suitable for the systematic review methodology. The review question and objectives bring structure and focus to the important elements of the topic. The whole review team should be involved in development of the objectives to ensure that both methodology and content knowledge are taken into account.

The objectives will be used to determine:
• Eligibility criteria
• Search strategies
• Data collection
• Data synthesis

The systematic review objective is usually a single sentence based on your review question and supported by the background section. Different frameworks can be used to help formulate your research question. The PICO framework is most commonly used for intervention systematic reviews. Other frameworks are available for different review types.
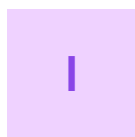
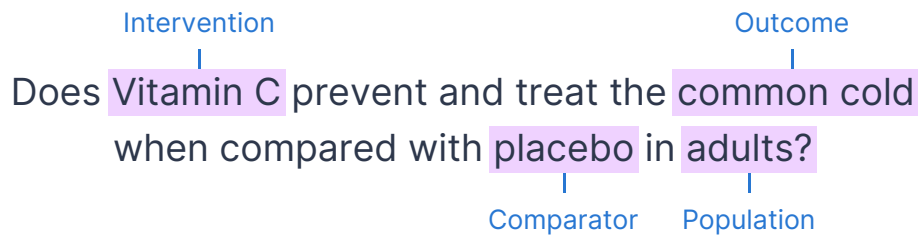| **P**	**I**	**C**	**O**	**T**
Population	**Intervention**	**Comparison**	**Outcomes**	**Timepoints**

Primary objective

The primary objective is usually framed by the PIC(O) components, primarily Population, Intervention and Comparison. The objective can include outcomes where appropriate.

> 📄 **Common format used by Cochrane**
>
> To assess the effects of **[intervention or comparison]** for **[health problem]** for/in **[types of people, disease or problem and setting if specified].**

Intervention   Outcome

Does <mark>Vitamin C</mark> prevent and treat the <mark>common cold</mark> when compared with <mark>placebo</mark> in <mark>adults?</mark>

Comparator   Population

If the review will investigate multiple interventions then the protocol should explain how these will be addressed within the review objectives. Consider if you will report on each intervention separately, if the interventions will be combined in the summary, or if you plan to compare them directly.

📄 **Example primary objective/s:**

To establish if oral Vitamin C supplementation reduces the incidence, duration and severity of the common cold when used as a preventative strategy or at the onset of symptoms.

What about secondary objectives?

Secondary objectives might explore specific settings, specific groups of participants, cost-effectiveness or qualitative themes and should be listed below the primary objective.

📄 **Example secondary objective/s:**

To investigate sub-populations that may have greater benefit than the general population with Vitamin C supplementation.

Broad versus narrow reviews

Questions that are broad may result in large volumes of evidence which may be unmanageable. Additional resources may be required for searching, study selection and data extraction. However, because of the breadth of participant populations, the results may be more generalisable and provide a comprehensive summary of the evidence.

Questions that are narrow may miss potentially important studies or result in 'empty' reviews (no evidence identified). With narrower questions it may be difficult to explore any differential effect of an intervention for different populations or settings. However a narrower question may be more manageable for the review team.

📄 **Example broad versus narrow**

Broad: "Does vitamin C prevent and treat colds?"

Narrow: 'Does vitamin C (500mg daily) prevent and treat the common cold when compared with placebo in adults aged 65 years or older?'

Splitting large reviews

Sometimes, as the review gets underway, the review team may decide that the review will be too large or unwieldy and that a better approach would be to split them. In these circumstances, a new protocol should be developed for each review.

05
Methods

Eligibility criteria for selecting studies (study characteristics)

It is critical to provide details of the eligibility (inclusion and exclusion) criteria for your review for transparency, determining applicability and comprehensiveness. The eligibility criteria will be used to help you decide on which studies to include and exclude. Describing the eligibility criteria can help develop the search strategy and will be used during study selection/screening.

Frameworks

When developing your eligibility it is important that the entire team is clear on the criteria. Clarity on how eligibility criteria are applied is essential for consistent application by the research team.There are many frameworks that can be used to establish your eligibility (inclusion and exclusion) criteria and inform your search strategy. The most commonly used framework for intervention systematic reviews is:
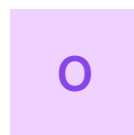
P	I	C	O	T
Population	Intervention	Comparison	Outcomes	Timepoints

You might want to add the setting or context, or the study design to your eligibility criteria.

Population (Participants, people, sample)

Summarise the characteristics of the population that are being studied in your review and those you want to exclude, taking equity and special populations into consideration. This might include age, gender, ethnicity, health-, economic- or other relevant status, as well as the impact of outcomes on different population groups.

> 📄 **Example population**
>
> **Inclusion:** We will include adults, 18 years of age and over.
> **Exclusion:** We will exclude children <18 years old.

If your review is looking at a population with a specific disease, stage of disease or disease severity then you will need to provide clear details of these criteria. You should provide clear rationale for any limits that you place on your population of interest. Do you think that the group with a specific disease severity will respond differently to the intervention compared with the population with that disease?


📄 **Consideration**

Definitions may differ on a geographic basis or may have changed over time. Older studies may have used different diagnostic tests or criteria compared with current studies.

If the population of interest that you are looking at is more general, or you are looking at a population with a general health condition, then less detail is required.

Plan what to do if a study has mixed data

Describe what you will do in situations where mixed data might be reported but are not separated by population group. E.g A study reports both adults and children but your review is only focused on adults or your review is focused on adults aged less than 80 years but some studies include adults up to 90 years.

Adults   Children   Mixed data
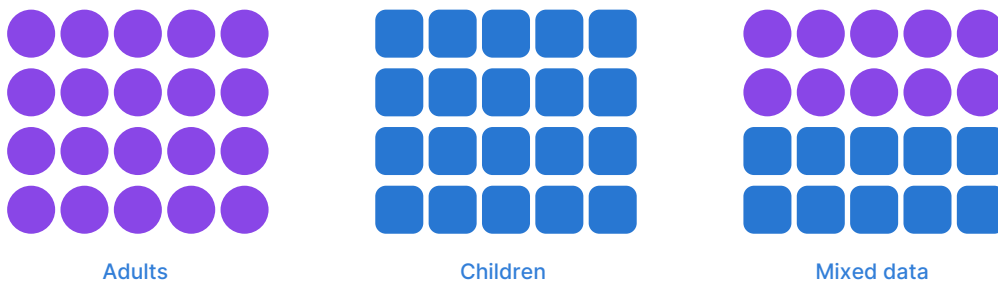
In these situations, you could propose that:

- You only collect the data for the relevant population and exclude data from ineligible populations. However, these specific data may not be available in the publication. You could propose that you will attempt to contact the study authors for more details.

- You could include the study. Although not all of the participants will be eligible for your review, you would not lose any important data. Some review teams set a threshold for inclusion. For example if 70% or more of the population was eligible for inclusion, all data will be included. You may want to conduct sensitivity analyses on these studies during the analysis phase of the review.

- You could exclude the study. However, you may lose important data about the population that was eligible for inclusion. The review team will need to consider the risk-benefit ratio of excluding these studies.

Types of intervention

Give a clear and detailed description of the intervention of interest in your review. There needs to be sufficient information to discriminate between your intervention and others that are outside the scope of your review. You should include, where appropriate:

- Drug name (generic and brand names)
- Dose administered
- Dose of administration and frequency of administration for a pharmacological intervention
- Name of procedure and route of approach for a surgical intervention

Behavioural and complex interventions with multiple components should be described in detail for each component. Detail how and where the intervention is delivered and by whom. Provide details of any co-interventions that will be included in your review.

Be precise when describing complex interventions such as those with multiple components for example behavioural, community-based or educational interventions. There will be inter-study variation in the literature. Each study may have slightly different components or regimens that may not always be clearly described. Clarify the components or combinations essential to your review intervention, and any that should be excluded.

It is also important to consider how your intervention of interest might be applied geographically and in different contexts. Are there likely to be any variations of the intervention based on context?

📄 **Example intervention**

Inclusion: We will include studies administering oral Vitamin C (ascorbic acid) of any dose.
Exclusion: We will exclude studies administering intravenous Vitamin C (ascorbic acid) and studies using combination therapy.

Types of comparison (comparators, control)

Give details of the comparison to the main intervention in your review. The comparison should be based on the review objective. This might be another intervention, exposure or phenomenon of interest. It might be a usual care, untreated or unexposed group, or a placebo group. Provide a clear and detailed description of the comparator group(s).

📄 **Example comparison**

Inclusion: We will include studies where the comparison is an inactive placebo.
Exclusion: We will exclude studies where a combination therapy is also administered with the placebo.

Types of outcome measures

Outcomes do not always form part of the eligibility criteria for a review, as this may make it difficult to assess the risk of publication or dissemination bias. However, you should identify in advance the outcomes you plan to assess in your review. This will minimise bias in the selection of outcomes when you complete the review.

Studies that do not measure your outcomes of interest should still be included in the review, although they cannot contribute to your analysis of those outcomes. It is important to include these studies so that you are presenting a complete picture of the literature. Provide a clear justification if you choose to exclude studies that did not report, or include, a specific outcome of interest as the review may be interpreted as being biased through selective reporting.

List the outcomes you are interested in measuring or evaluating. These can be clinical outcomes, patient-reported outcomes, adverse events, or any relevant endpoints. Consider including outcomes that matter to the consumer as well as the decision makers/ healthcare professionals.

Primary vs secondary outcomes

Most systematic reviews include primary (critical) and secondary (important) outcomes which are used when evaluating the overall impact and effectiveness of the intervention. Focus on the outcomes that are most relevant to your review to avoid collecting unnecessary information and drawing conclusions from underpowered data.

- **Primary or critical outcome/s** are the most important and relevant outcomes for the review. They are usually chosen as the main measures of effectiveness for the intervention and should include at least one potential benefit and harm (adverse effect). If you plan to explore the certainty of evidence (with GRADE for example), the outcomes that will be reported in the Summary of Findings table should be clearly identified.

- **Secondary or important outcome/s** provide additional information about the effectiveness of an intervention and often about the harms, quality of life, or cost-effectiveness.

📄 **Example outcomes**

Primary/critical outcomes:
- Duration of cold (days of illness)
- Severity of cold (reported as symptom severity score)

Secondary/important outcomes:
- Presence of symptoms including cough, sore throat, fever, chills
- Absence from workplace or education setting (days)
- Adverse effects
- Medication adherence as measured by tablet count

Primary vs secondary outcomes

The breadth of the outcome is dependent on the review question. The key is to find a balance by planning ahead and involving experts.

- **Broad outcome**: A lot of outcome data will be extracted from studies. The more data you extract, the more heterogeneity you're likely to encounter, which can affect your analyses and interpretations. Some data you extract might not be relevant to the review question.

- **Narrow outcome**: Fewer outcome data will be extracted across studies as it is recognised that only some of it is relevant to the review question. This will minimise variation, but give you a lot less information.

Consider how the outcome is reported

Outcome reporting is not the same in all studies. For example, adherence to medication could be self-reported, measured by tablet count or measured in serum levels. Deciding to collect all the data reported in this case could risk over-representing the impact of the outcome.

Combining data may not be feasible, especially in complex interventions with many reported outcomes. Lumping outcomes together may dilute the effect and make them less meaningful.

One option is to select which measure will be used for the purposes of analysis and which measures will be reported narratively (without statistical analysis), where data are available. This should be decided by consensus within the review team or based on which measurement is most 'clinically' important, or based on objective (serum levels) rather than subjective measures (self-reported usage).

Timepoints/endpoints

If appropriate, you should pre-specify the timing of outcome assessment. Some reviews include all time points reported in the included studies, other reviews are more specific (e.g. end of treatment, 6 months, 12 months). Consider how you will handle data that do not easily fit into one of your pre-specified categories. Will you plan to group timepoints together?

📄 Example timepoints

Outcome data will be recorded at the following timepoints (or closest time point) where data are reported:
- Baseline
- 3 months
- 6 months
- 9 months
- End of treatment

Setting/context

Where appropriate, summarise the setting or context of the review. Is your review focused on community or hospital settings, education or business settings? There might be a specific political, cultural or socio-economic focus.

📄 **Example setting**

Inclusion: We will include studies in community-based settings.
Exclusion: We will exclude studies in hospital, or clinic-based settings.

Study design/types of study

Give clear and unambiguous details of the study design/s you plan to include in your review, even if there are no restrictions. Detail any designs you plan to exclude or if you plan to include a mixture of quantitative and qualitative designs.

If you intend to include only randomised controlled trials (RCTs) then you need to state clearly that you will exclude other 'high-risk' quasi-randomised and non-randomised study designs. Alternatively you could include both randomised and quasi-randomised studies and only include RCTs in the meta-analysis or use sensitivity analysis to investigate the robustness of the meta-analysis results based on methodological limitations. You will need to clearly explain this here and in the methods section.

For some interventions RCTs are impractical, not possible or unethical. However, the inclusion of other study designs can introduce higher risk of bias and should be avoided where possible. Clearly define and provide a rationale for using any other study designs.

📄 **Example RCT only**

Inclusion: We will include randomised controlled trials (RCTs).
Exclusion: We will exclude all studies rated as 'high-risk' of bias for random sequence generation.

📄 **Example RCT and Quasi-RCT**

Inclusion: We will include both randomised controlled trials (RCTs) and quasi-RCTs (where randomisation was attempted but was subject to potential manipulation, e.g allocation by day of the week, date or birth) as we anticipate that few, if any, true RCTs will have been conducted in the [enter area of research].
Exclusion: We will exclude all studies rated as 'high-risk' of bias for random sequence generation except quasi-RCTs.

✏️ Changing or amending eligibility criteria

- Provide a rationale for any changes to eligibility criteria
- Any changes to eligibility criteria should be consistently applied to all studies assessed for inclusion
- Do not make changes to the protocol based on the results of the review
- Making changes to the eligibility criteria may affect your original search terms. Consider re-running the search to ensure you have not missed any relevant studies

💡 Useful tools:

The TIDieR checklist can be used to help write a detailed description of interventions of interest in your protocols.

Eligibility criteria for selecting studies (report characteristics)

In addition to the study characteristics, the report characteristics can be used to select studies for inclusion or exclusion. Always provide a justification for any limitations you impose on the body of available evidence. Limitations may affect the interpretation of the evidence and the generalisability of the findings.
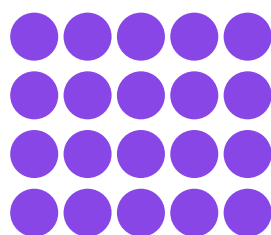
No limitations/filters
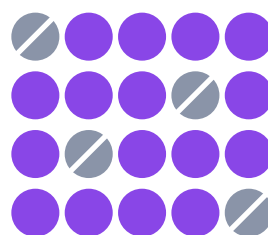
Limitations/filters applied

Some common report characteristics include:

- Publication years
- Language
- Publication status
- Geographical location
- Type of publication

Publication years

The protocol should state if the search will be unrestricted by year of publication or if limitations will be put in place. This aids the transparency and reproducibility of the review.

Some reviews limit publication years for the following reasons:

- **Relevancy**: There is no need for literature searches to precede the availability of an intervention or technology. Limiting publication dates can ensure that the study data reflects current rather than outdated practice which will not be useful or relevant to the review.

- **Resource efficiency**: Some systematic reviews end up with a large volume of studies for inclusion which can be unmanageable for the review team. Restricting the publication years can help streamline the screening process by reducing the number of older studies that need to be assessed for relevance. However, limiting the publication years based solely on the volume of studies could introduce bias to the review and needs to be justified.

Limiting the publication years of the review may have implications for the comprehensiveness and generalisability of the review findings.

> 📄 **Example publication years**
>
> There will be no restrictions based on the year of publication.
> Or
> We will search databases from inception to the search date.
>
> Example: As xxxx intervention/drug first appeared in the market in 2001, we will restrict the year of publication from January 2001 up to the search date based on relevancy.

Language

The protocol should detail any limitations based on the language of publication. If other languages are included, the protocol should detail how these will be translated (translator; App). Data extraction of studies in languages other than those of the review team may be time consuming, expensive and introduce unconscious errors and misinterpretation.

Some reviews limit language of publication for the following reasons:

- **Resource/time constraints**: Limiting the review to publications in specific languages can help manage financial resources, particularly when translation services may not be readily available or feasible. It may be necessary to limit language of publication in a rapid review where there are time constraints.

- **Relevance**: Some teams may prioritise particular languages due to the relevancy of the review topic, setting or population.

Restricting the language of included studies is likely to introduce bias, especially if relevant studies published in other languages are excluded. The review team should carefully consider the potential impact of language restrictions on the comprehensiveness and generalisability of their findings. Justify any language criteria applied in the systematic review protocol.

> 💡 **Tip**
>
> Rather than excluding studies based on language of publication at the search stage, an alternative is to exclude them during full-text screening. This provides transparency as to the volume of studies and allows the team to revisit them if required.

📄 Example language

There will be no limitations based on language of publication. We will use Google Translate in the first instance to try and extract relevant details and data.

We will limit studies to those published in the English language. Studies published in other languages will be excluded at the full-text stage.

Publication status

The protocol needs to clearly detail any limitations on the publication status of included studies and provide a rationale. Some reviews include full publications only and exclude conference abstracts and preprints because including unpublished studies can introduce bias. However, this approach could itself introduce bias by missing potentially relevant information.

Some reviews limit publication status for the following reasons:

- **Quality assurance:** Research teams may limit their reviews to peer-reviewed studies, with the aim to include higher-quality evidence in their synthesis. Grey literature, conference abstracts and unpublished studies may not have undergone the same level of peer-review as articles published in journals.

- **Resource/time constraints**: Some rapid reviews, where time is short, may limit the review to peer-reviewed publications to make the process more manageable for the team.

Restricting the review to peer-reviewed publications may have limitations. It could lead to the exclusion of valuable evidence such as preliminary findings, ongoing research, or studies with negative results. Review teams should carefully weigh up the potential benefits and drawbacks of publication status restrictions based on: the research question, the availability of evidence, and the desired scope and quality of the systematic review. Transparent reporting of eligibility criteria is essential to ensure the credibility and reproducibility of the review findings.

> ### 💡 Tip
>
> Rather than planning to exclude studies based on publication status, the protocol could plan to include all relevant evidence but include only the high-quality evidence in the meta-analysis and give a narrative summary of the other data.
>
> Have a plan for who will follow-up any missing information with primary authors of publications including the time allocated for responses and the number of requests sent.

> ### 📄 Example publication status
>
> Example: There will be no limitations based on publication status.
>
> Example: As this is a rapid review, we will only include peer-reviewed publications. We will exclude grey literature, conference papers and other unpublished literature or studies.

Geographical location

Some reviews focus on a specific geographical location of interest and consequently restrict studies to those that were conducted, or are concerned with, that location.

Some reviews limit geographical location for the following reason:

- **Relevance**: Limiting the included studies to those conducted in specific geographical locations means that the review findings are relevant to the population, exposure or context being investigated. There may be specific cultural, socioeconomic or environmental factors of interest. Some interventions may not be available in some geographical locations and the review may limit the search to exclude those locations. The findings may not be generalisable to other settings.

However, restricting geographical location may limit the breadth and diversity of the evidence base, potentially overlooking valuable insights from other settings.

Sometimes studies report geographical location as a city, state or region rather than a country. Limiting the search to a specific country/countries could miss these studies.

The protocol should justify any limitations based on geographical location. Transparent reporting of inclusion criteria is essential to ensure the credibility and reproducibility of the systematic review.

📄 **Example geographical location**

Example: There will be no restrictions on the geographical location in this review.

Example: This review will only include publications of studies conducted in Australia as this is the health-care setting of interest in this review.

Type of publication

Some reviews exclude specific types of publications such as letters, commentaries, press releases, and editorials.

Some reviews limit type of publication for the following reasons:

- **Not reporting primary evidence**: Letters, commentaries, and editorials often do not include empirical evidence from primary studies and may not contain relevant data that could be added to the body of evidence.

- **Risk of bias**: Letters and commentaries inherently have a high risk of bias. They lack methodological rigour, detailed reporting, and validation of results and are more likely to be personal reflections or opinions.

Some letters contain primary data and along with commentaries can contain unique insights which are relevant to the review topic. Before limiting the type of publication, consider whether they might contribute to the review's objectives. The protocol should justify excluding studies based on type of publication.

📄 **Example type of publication**

Example: There will be no limitations based on type of publication.

Example: We will exclude letters, commentaries, and editorials which do not include relevant primary empirical data.


💡 **Tip**

If you have a very large output from your search, you might decide to:

- Introduce some justifiable limitations
- Split your research question into more manageable focused questions
- Reconsider your choice of systematic review to answer your research question.

Eligibility criteria are important for developing search strategies

Clearly defining the eligibility criteria are important when planning and developing search strategies in systematic reviews. The eligibility criteria guide the development of search strategies by detailing the types of studies relevant to the review. This facilitates the creation of focused search terms and filters which result in targeted and relevant outputs.

P I C O T	→	🔍	→	⬤⬛⬛⬤⬛ ⬤⬤⬛⬤⬤
Eligibility criteria		**Search strategy**		**Potential studies**
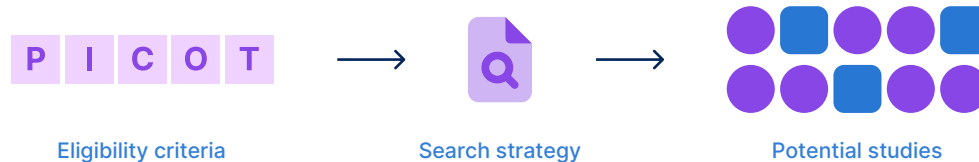
Eligibility criteria are important for developing search strategies for the following reasons:

- **Improving precision**: Pre-specifying the inclusion and exclusion criteria in the protocol can help the research team to design search strategies that target relevant studies. This will not only significantly reduce the retrieval of irrelevant articles but also improve precision and efficiency during screening.

- **Improving sensitivity**: Detailing the eligibility criteria in the protocol will identify populations, interventions, outcomes, settings and study designs that should be included in the search strategy. A comprehensive and sensitive search will maximise the chances of capturing relevant studies.

- **Facilitating Boolean logic**: Boolean operators (AND, OR, NOT) can be used to narrow or expand search strategies when eligibility criteria are clearly defined in the protocol.

- **Optimising transparency and reproducibility**: Review methodology is reproducible when eligibility criteria are used to inform the search strategy. The team can easily report how the search was constructed based on pre-specified criteria. It also ensures that other researchers can replicate the search or update the review.

Search methods for identification of studies (sources)

The foundation of a robust literature review is a well developed search strategy and identifying the sources to conduct your search. The protocol should clearly identify all sources that will be searched including databases, registries and other sources as well as the date range of the search (start and end date) and the search platform provider (e.g. OVID or PubMed).

Bibliographic database searching

A comprehensive search of several bibliographic databases is an efficient foundation to identify relevant literature for your review. It is recommended to search a minimum of two databases when conducting a systematic review [Note that some databases require payment to access and access may vary by institution/organisation. Check with your librarian for additional information]. The databases you search will largely depend on the topic of your research.

For an intervention systematic review in the Medical and Health Sciences field, the Cochrane Handbook for Systematic Reviews and Interventions (Section 4.3 "Sources to Search") identifies 3 key databases:

- MEDLINE (commonly searched via PubMed, Ovid, or EBSCO)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- EMBASE (Excerpta Medica dataBASE)

Other subject-specific databases can and should be searched based on the topic of the review question. These include but are not limited to:

- PsycINFO for the fields of psychology and psychiatry
- ERIC (Education Resources Information Center) for the education field
- CINAHL (Cumulated Index to Nursing and Allied Health Literature) for nursing and allied health literature
- Web of Science primarily covers science, social science and arts, and humanities.

There are regional databases available which may be useful to some searches including:

- LILACS (Latin American and Caribbean Health Sciences Literature) covers technical-scientific literature in Latin America and the Caribbean

- CNKI (China National Knowledge Infrastructure) covers Chinese scholarly articles

Citation searching

In addition to searching bibliographic databases, research teams may utilise citation searching to locate relevant sources. The most basic form of citation searching checks the reference list of relevant articles that have been identified. There are tools that allow for "forward" citation searching. Forward citation searching, also known as "cited by," is available in Google Scholar, Web of Science, and PubMed. It is also possible to utilise the "similar article" or "related article" links in these sources.

Grey literature searching

You may plan to search for grey literature sources. According to the National Library of Medicine, grey literature is defined as

'information produced on all levels of government, academia, business and industry in electronic and print formats not controlled by commercial publishing i.e., where publishing is not the primary activity of the producing body.'

Grey literature broadly includes:

- Reports
- Theses and dissertations
- Conference proceedings
- Standards
- Technical documentation
- Datasets
- Preprints
- Web content
- Government documents.

Sources to search for grey literature include Google Scholar, Proquest Dissertation and Theses, and professional organisation and association websites.

Registries

Trial registries can provide useful information and data associated with ongoing, completed and terminated trials and studies. The most commonly used registries include:

- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)

Regulatory sources and clinical study reports

Some review teams may plan to search regulatory agency sources for further information on clinical trials such as clinical study reports. Clinical study reports are detailed reports of clinical trials often submitted as national or international drug marketing and authorisation applications. They can include details of methods and key results. Common sources include:

- Australian Therapeutic Goods Administration
- European Medicines Agency
- Health Canada
- US Food and Drug Administration

📄 **Example search plan**

We plan to search the following databases and sources from inception to 1 June 2024:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE via PubMed
- CINAHL
- Web of Science
- EMBASE

We will also screen the reference lists of included studies and search U.S. National Institutes of Health trials register www.clinicaltrials.gov and the WHO ICTRP www.who.int/ictrp.

💡 **Tip**

Searching multiple and different sources to identify relevant evidence reduces the risk of bias and the risk of missing studies.

Search methods for identification of studies (strategy)

It is important to **consult with a Librarian or Information Specialist** when developing a search strategy. This section of "Search methods for identification of studies" is meant to start you off in the right direction so when you meet with your Librarian, you can maximise the value of that conversation.

High-quality and accurate searches are key to identifying the relevant literature. Making errors in the search strategy can result in missing potentially relevant studies or retrieving irrelevant studies. The protocol should include a draft search strategy for at least one major database.

After developing the research question, it is time to build the search strategy using keywords and controlled vocabulary combined with Boolean operators, search filters and sometimes limitations. Refer to the review eligibility criteria when developing the research strategy.

Some teams find it useful to conduct a '**scoping**' or '**pilot**' search, as an informal way to:

- Identify the literature already published
- Develop and refine the review question and PICO criteria
- Verify that there is not an existing review on the topic

Controlled vocabulary

Many bibliographic databases have a resource for controlled vocabulary. A controlled vocabulary thesaurus can help:

- Assist in the development of synonymous keyword terms
- Inform you of "official" medical terminology
- Inform you of how a term fits into the bigger picture of the concept
- Build a search specifically with controlled vocabulary terminology

The controlled vocabulary thesauruses in PubMed and EMBASE are called MeSH and EMTREE, respectively. Controlled vocabulary is unique to each database because of differences in indexing.

Search filters or hedges

Another strategy is identifying search filters or hedges. Search filters and hedges are a pre-defined or validated combination of search terms used to retrieve journal articles. ISSG Search Filter Resource contains validated search filters. The Cochrane Handbook (section 4.4.7) contains Cochrane Highly Sensitive Search Strategies. McMaster University Health Information Research Unit developed a "Hedges Project" to assist in locating search hedges.

Keywords and Boolean operators

A search strategy will contain a combination of keywords and controlled vocabulary. Keywords are the main points and words from the research question or PICO criteria. Controlled vocabulary are pre-defined terms indexed to retrieve content. Boolean operators are words and symbols used to combine or limit words and phrases in a search strategy and include:

- **AND** - narrows search
- **OR** - expands search
- **NOT** - narrows search by excluding a term
- Truncation and wildcards *** $?** - expands search
- "Exact phrase search" - narrows search to a specific word phrase

---

📄 **Example keywords and boolean operators**

The following strategy will be used to search MEDLINE and will be adapted for the other databases:

1 Common Cold/
2 common cold*.tw.
3 Rhinovirus/
4 rhinovir*.tw.
5 coryza.tw.
6 "acute rhinitis".tw.
7 ((viral or virus*) adj2 rhinit*).tw.
8 or/1-7
9 exp Ascorbic Acid/
10 ascorb*.tw,nm.
11 (vitamin* adj5 c).tw.
12 or/9-11
13 8 and 12

Source: (Hemilä & Chalker, 2013) Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD000980. DOI: 10.1002/14651858.CD000980.pub4. Accessed 05 May 2024.

Data management and study selection (screening)

The use of systematic review software and reference management software is becoming increasingly widespread.

Web-based platforms, such as Covidence, can assist review teams with tasks including: the importation and deduplication of references, screening of articles, importing of full-text articles, creation of PRISMA flow diagrams, data extraction and data export.

Commonly used reference management software include: Endnote, Zotero, Mendeley and RefWorks. These tools can be used to deduplicate references, locate and store full-text articles and screen studies. Other data management tools may include Excel or Word documents.

You should describe if your team plans to use systematic review software, reference management software or any other tool to manage any stage of the review process. The description should contain sufficient detail that the process could be replicated if needed, including any relevant version number.

> 📄 **Example software**
>
> We will use Endnote 20 reference management and Covidence systematic review management software.
>
> **Endnote 20** will be used to store references identified from searching and full text articles.
>
> **Covidence** will be used for de-duplication, screening, quality assessment and data extraction.

Describe procedure for selecting studies

❝ Decisions about which studies to include in a review are among the most influential decisions that are made in the review process and they involve judgement. ❞

- Cochrane Handbook 4.6.4

The protocol should describe the approach that will be used to identify potentially relevant studies (title/abstract screening) and select included studies (full text screening).

Merge search results and identify duplicates

Explain how the search results from multiple sources, registries and databases will be merged. Will you use a reference manager or systematic review management software?

The protocol should explain how duplicate publications (i.e. records reporting the same journal title, volume and page numbers) will be handled and reported.

- Will they be screened manually? If so, how many reviewers will check for duplicates?
- Will they be screened using systematic review management or reference manager software? If automated deduplication is used, will the excluded references be checked, and if so by how many reviewers?

Duplicates can be found before screening starts and at any time during screening and data extraction. Detail how manually identified duplicates will be handled and reported.

The protocol should detail that the number of duplicate records will be reported in the PRISMA flow diagram (or similar figure) and how they will be reported. Consider reporting the number of duplicates identified prior to screening and those identified manually during screening/data extraction. You might decide to report those duplicates identified by automation tools and those identified manually.

📄 **Example duplicate handling and reporting**

Duplicates identified pre-screening: We will use Covidence systematic review management software for the deduplication of all references imported to the software. MM will manually screen duplicates. Any non-duplicates identified will be returned to the pool of studies for title and abstract screening.

Duplicates identified during screening/extraction: Studies identified as duplicates during screening or data extraction will be manually identified as duplicates. We will report these separately from duplicates identified by automation tools in the PRISMA flow diagram.

Screen titles and abstracts

The protocol should document if one or more reviewers will be involved in screening studies at both title and abstract and full text stages. Names of the reviewers allocated to these tasks should be included, where possible. It is strongly recommended that where possible two independent reviewers undertake screening to ensure objectivity is maintained and to reduce the risk of bias. Where screening is undertaken in duplicate by independent reviewers, the protocol should detail the process for resolving conflicts or discrepancies (e.g. involve a third reviewer for arbitration, contact original authors). Due to time or financial constraints it is not always possible for all studies to be screened by two independent reviewers. Clearly detail in the protocol if you plan to conduct proportional screening (e.g. 20% screening with dual reviewers and the remainder screened by single reviewer).

> 📖 **Cochrane recommends:**
>
> "Use (at least) two people working independently to determine whether each study meets the eligibility criteria, and define in advance the process for resolving disagreements."
> Cochrane MECIR Manual, C39

Title and abstract screening aims to remove irrelevant studies and publications. Document if screening will be by combined title and abstract or title followed by abstracts separately. The protocol should document if one or two independent reviewers will undertake the initial screening and if the screeners will be blinded or not. The protocol should detail if piloting will be undertaken. Piloting will help to ensure that the screening team understands any nuances of the eligibility criteria as they relate to the research question.

The protocol should detail the judgements to be used during screening (Yes, No, Maybe/Unclear). Having an option for Maybe/Unclear allows for the full text to be retrieved for that study to confirm eligibility for inclusion in the review.

Conflicts can arise during title and abstract screening (conducted by two reviewers) when one reviewer votes Yes and the other reviewer votes No; or when one reviewer votes No and the other reviewer votes Maybe/Unclear. The protocol should explain how these conflicts will be resolved. Will the reviewers discuss the conflicts and come to a final decision? Will a third party resolve all conflicts? Will a third party only be involved where arbitration is required?

Retrieve full text and link together multiple reports

In order to conduct full text screening it is important to retrieve as many full-text articles as possible via reference management software and library resources. The protocol should explain the process for full text articles that cannot be retrieved, due to access or financial constraints for example. You can plan to report the number of articles sought for retrieval and those retrieved in the PRISMA flow diagram.

Some authors publish the same data multiple times which can introduce bias and potentially result in double-counting of participants to the review. Describe any steps that will be taken to avoid this scenario. This can include checking for the same authoring team, sample size and study location or study registration number. Check for any differences in key characteristics or outcomes between these publications, you may need to confirm data with the authoring team.

Some studies can have multiple publications that include study registration, study protocols, conference abstracts, interim and final reports. These studies may report on different sample sizes. To avoid double-counting of participants, it is important to identify which primary publication will be used to provide the data in the review. This may be the most recent or comprehensive publication. Other publications relating to the same study should be merged or linked together. The PRISMA flow diagram will identify how many reports/publications were associated with the number of studies in the review. To identify multiple publications of the same study check the authoring team, location, and study registration number, where reported.

Full text screening

Full text screening is the process used to select the studies for inclusion in the review and is based on a thorough assessment of the full text article using the review eligibility criteria. The protocol should document if one or two independent reviewers will undertake the initial screening and if the screeners will be blinded or not.

The protocol should detail the judgements to be used during screening. For full text screening, these are usually include and exclude. If a study is excluded during full text screening a clear reason should be provided. The reasons for exclusion should appear on the PRISMA flow diagram.

Two types of conflicts arise during full text screening. The first is when one reviewer votes to include and one votes to exclude a study. The second conflict can arise when both reviewers have voted to exclude a study but provide differing reasons. Only one reason per study can be added to the PRISMA flow diagram. The protocol should explain how these conflicts will be resolved. Will the reviewers get together and discuss the conflicts and come to a final decision? Will a third party resolve all conflicts? Will a third party only be involved where arbitration is required?

The protocol should detail any attempts to contact original authors to obtain clarification of data. For those studies that remain incomplete/unobtainable the protocol should detail that the studies will be identified as incomplete. Some reviews list these studies in a table of 'Characteristics of studies awaiting classification'.

If you plan to search trial registries then the protocol will need to explain how these studies will be recorded and documented. These studies are often identified as 'ongoing studies' and are summarised in an 'ongoing studies' table. Studies can also be identified that are completed but the data have not been published or reported. The protocol should detail if these studies will move into 'awaiting classification' or will be dealt with in another manner.

> 📄 **Example**
>
> MM and GG will independently review full text articles for inclusion or exclusion and record exclusion reasons. Where disagreements can not be resolved, HH will act as an arbitrator and make the final screening decision.

Inter-rater reliability (optional)

Inter-rater reliability is the level of agreement between the screeners and is reported as a Cohen's kappa value. The protocol should detail if inter-rater reliability will be reported and if this will be calculated on all screening or a proportion of the studies screened. Provide a rationale for only reporting on a proportion of studies. Explain what the process will be if the Cohen's kappa value is low. You could, for example, revisit the eligibility criteria or provide more training to the screening team.

📄 **Example inter-rater reliability**

Inter-rater reliability will be assessed after 20% of studies have been screened at both title and abstract and full text screening stages. If Kappa score is <0.5, we will explore potential reasons and reassess Kappa after changes have been implemented.

💡 **Tip**

Providing a **hierarchy of reasons for exclusion** in your protocol can save time when screening. It helps the review team consistently select reasons for exclusion and reduce the number of conflicts where both reviewers exclude a study but give different reasons.

Data extraction and management

Data extraction is a process within a review workflow in which review teams collect relevant information from included studies, and organise it in a way that enables them to make use of the data in future stages.

Planning data extraction and synthesis at the protocol stage can help to ensure the process is:
- Rigorous, transparent and reproducible
- Done in a way that reduces errors and bias (e.g blinding and duplication)
- Documented clearly

Data collection

Define the data items to be collected for study details, methods, populations, interventions, outcomes, and timepoints to save time and avoid over-extraction (collecting more data than you need). If you have used a framework (e.g. PICO) to create the research question, this can guide what data to collect.

The data items you intend to collect should allow you to effectively compare studies without needing to revisit the original source because you didn't extract the data you need.

For example:
If you intend to compare a particular outcome at 8 weeks or the closest time point, then only collect the result data at this time point instead of all intervals reported in the study.

For more information, refer to the 'Finding the balance' section of 'A practical guide to Data Extraction for Intervention Systematic Reviews'.

Data management

Describe how data will be managed. Consider if you will use paper templates, electronic templates or systematic review software to collect data.

📄 **Example data management**

We will use Covidence systematic review software to create a data extraction template to capture relevant data.

We will use an Excel spreadsheet to create a data extraction template to capture relevant data.


Creating a template

Planning a well-defined data extraction approach before starting the extraction process is crucial. This will minimise the need for rework, mitigate unforeseen circumstances, and address uncertainties. A good data extraction template means that you should not have to go back to the original source. You will have recorded everything you need for subsequent analysis or synthesis and interpretation. You may want to consider any planned subgroup analysis (e.g. sex, dosage, mode of administration) as you design the subsections of the template.

You can find a link to a draft template example here.

Why piloting is important

Piloting is the process of completing data extraction for a select number of studies to evaluate the process before extraction starts across all studies.

Studies to extract   Pilot and edit extraction template   Extract all studies with finalised template
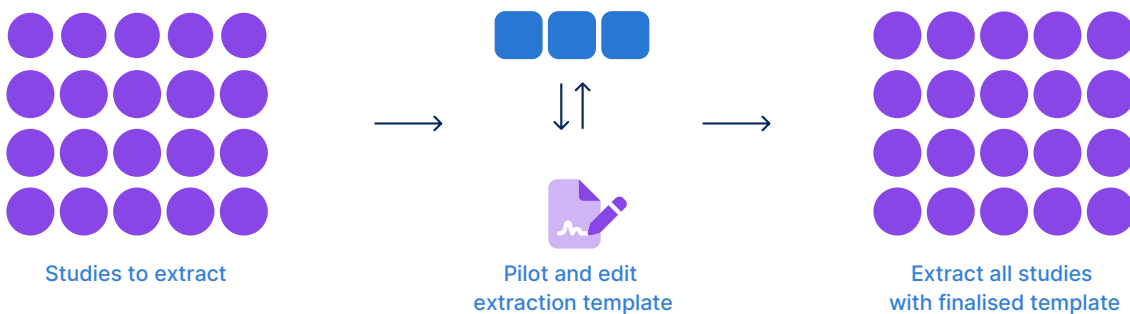
The objective is to assess the effectiveness of the extraction template that has been developed, to ensure that:

- The template's layout and sequence are logically organised.
- Any missed or irrelevant data points are identified early.
- The guidance and/or instructions for extractors are as comprehensive as possible.
- Extractors have had enough training to perform extraction effectively.
- The anticipated output will enable you to compare and group studies so you can
- analyse results for your review.

Additional information and tips on piloting can be found in A practical guide - Data Extraction for Intervention Systematic Reviews

Number and blinding of data extractors

In the protocol, describe who will extract data. This should include the number of extractors and any procedures for resolving conflict/s. Indicate if data extraction will be blinded.

📄 **Example blinding**

Two reviewers will conduct data extraction independently. We will resolve conflicts by consensus. Where conflicts cannot be resolved, a third reviewer will act as an arbitrator.

Describe plan for quantitative synthesis

Diversity within populations, interventions and/or outcomes can restrict or prevent the ability to conduct meta-analysis. It is important to set out the criteria that need to be present for data synthesis to proceed. Consider if there are mixed populations or different drug doses or study designs that might introduce heterogeneity to the data.

Describe plan for retrieval of missing data

Dealing with missing or unclear data in a systematic review is a common challenge. Missing or unclear data may affect your final data and lead to misinterpretation as it's challenging to draw meaningful conclusions or incorporate them into the review. When you encounter this issue, it's essential to make efforts to obtain the missing data to ensure the completeness and accuracy of your review. One retrieval method is contacting the authors of the study.

The protocol should document if/how you will contact authors of primary studies to request additional information or data and any time frames to await a response.

📄 **Example missing data**

Where data are ambiguous or missing we will contact primary authors, where contact details are available. We will document these communications. We will use sensitivity analyses to evaluate potential effects of missing data, including study attrition.

Define unit of analysis

A unit of analysis issue can arise in a systematic review because of errors that are made in the definition of "who" or "what" are being analysed. It is important to specify the review's unit of analysis as this will influence the analysis and interpretation of the data.

The protocol should clearly define what the unit of analysis will be for the review or for each outcome if that differs. The unit most frequently reported is a person/participant. However, in some studies the unit of analysis could be a limb, a lesion, or an eye and one participant could therefore be randomised multiple times. In cluster-randomised studies, the unit of analysis could be the cluster (school, hospital, city, household).

> 📄 **Example unit of analysis**
>
> The unit of analysis in this review will be the participant.
> The unit of analysis for this outcome will be the patient.

Describe how multiple reports of same study will be handled

Reporting of multiple publications from the same study in a systematic review is a common scenario, especially when dealing with multiple papers or publications in different formats over time. Multiple publications could include primary research papers, conference abstracts, posters, personal correspondence or supplementary materials.

It is important to maintain the rigour of your review and to be transparent about how you handle these studies to avoid duplication of data and/or double counting of participants.

The protocol should explain how publications from the same study will be handled. Consider detailing how you will check publications are related. Related studies are usually merged - this means that there is one primary reference (usually the most recent or most complete) linked to other references. Any relevant data from the publications can be reported under the primary reference. If you are unsure if publications are linked to a specific study, contact the primary authors for more information.

> 📄 **Example multiple reports of the same study**
>
> We will identify and merge publications reporting on the same study. We will identify a primary reference for reporting purposes. If related references are suspected, we will check the following for confirmation:
> * Trial registration numbers
> * Study sponsors or Ethics Committee numbers
> * Location/s of where the study was conducted
> * Start date and duration of the study
> * Number of participants recruited and baseline characteristics
> * Author names

Describe assumptions and definitions

It is critical throughout the protocol to clearly define the key elements and describe any assumptions. Clear definitions of interventions, comparisons, populations, settings and outcomes will ensure that the review team accurately select studies and record data.

Useful resources

[A practical guide - Data Extraction for Intervention Systematic Reviews](#)

Data analysis/synthesis

You should have carefully planned and considered all the previous sections of the protocol before planning the data analysis.

Data analysis/synthesis is the process of investigating relationships between variables. This analysis can use statistical methods or can be narrative depending on the data extracted.

Statistical analysis

Studies to analyse

Narrative analysis
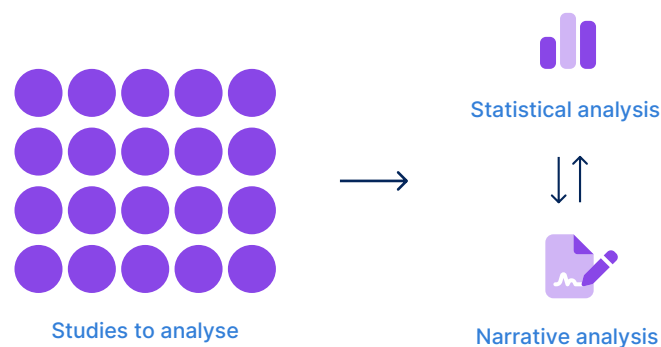
Statistical analysis

Describe the planned effect measures, statistical method and the statistical model.

- Effect measure - The choice is dependent on the type of data (continuous, dichotomous, time-to-event) and includes risk ratio, odds ratio, and risk difference for dichotomous data; mean difference and standardised mean difference for continuous data and hazard ratio for time-to-event data.
- Statistical method - this includes inverse variance, DerSimonian-Laird, Mantel-Haenszel, and Bayesian.
- Fixed- or random-effects models - A fixed-effects model assumes that there is homogeneity between studies and that any observed differences are due to sampling error. The model uses weighting and assigns greater weight to studies with smaller variances. A random-effects model estimates the average effect size for all included studies and accounts for both inter- and intra-study variability.

Any other planned analysis should be described such as cost-effectiveness or decision-making analyses.

Assessing heterogeneity

Heterogeneity is an indication of the amount of variability between the results of different studies included in the review. Assessing heterogeneity helps decide if it is appropriate to pool data in a meta-analysis. The I^2 statistic or Cochran's Q test are common methods for reporting heterogeneity.

Heterogeneity can be explored and potentially explained in subgroup analysis. By exploring subgroups such as different populations, techniques, or study designs it may be possible to identify factors that influence the results.

Heterogeneity can also be used for sensitivity analysis where studies that contribute to heterogeneity are excluded from analysis, for example. The protocol should detail any planned subgroup or sensitivity analyses.

Where heterogeneity is very high, meta-analysis may not be appropriate.

Heterogenous data   Homogenous data
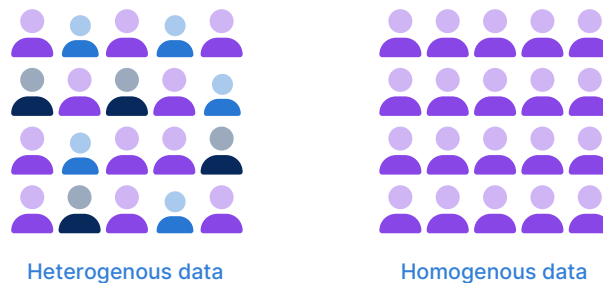
📄 **Example heterogeneity**

Where sufficient data are available for each outcome, we will use RevMan Web software to combine and calculate effect estimates. We will refer to the statistical guidance in the [Cochrane Handbook for Systematic Reviews of Interventions](#). We plan to report relative risk (95% confidence interval [CI]) for dichotomous data and mean difference (95% CI) for continuous data. We will use the Mantel-Haenszel method for the fixed-effect model if data are sufficiently homogeneous. Where data are heterogeneous (I^2=>/=50% or P<0.1) we will consider undertaking meta-analysis using a random-effects model. Where heterogeneity exceeds I^2 >/=80% we will not undertake meta-analysis but will narratively summarise the evidence.

Reporting data

Not all data in the included studies will be reported as you planned in the protocol. For example, the protocol may plan to record data as mean and standard deviation (SD). However, the data in studies may be reported as mean and standard error (SE) or median and range. The protocol should detail how such data will be handled. Consider:

• Converting data to the planned measure (convert SE to SD).
• Reporting data narratively/tabulated.

The protocol should outline if missing or unavailable data will be imputed. Caution should always be taken with this approach as you are making assumptions of the data. When imputing data, we recommend that you:

• Make a note of any data which have been imputed rather than extracted directly from a study.
• Include a footnote in the analysis, as appropriate.
• Speak to your review team, topic experts, statisticians before imputing data.
• Follow your review team's process on when or if to do this.

Sometimes outcomes can be reported using scales (e.g. quality of life, depression). However, some scales may report a higher score indicating a better outcome and others may report a lower score indicating a better outcome. You may need to consider planning to make adjustments to data so that the scales are aligned.

📄 **Example**

Where possible we will convert standard errors to standard deviations to allow data to be combined in meta-analysis. We will tabulate findings where data are reported as median, range or interquartile range and summarise narratively.

Choosing software for statistical analysis

The protocol should clarify which software (including name and version, if applicable) will be used to combine data and calculate any statistical analyses.

📄 **Example**

Summary statistics will be calculated using Excel 2021. Data for each outcome will be combined and the pooled analysis calculated using RevMan, according to the statistical guidelines found in the Cochrane Handbook Chapter 10: Analysing data and undertaking meta-analyses.

Subgroup and sensitivity analyses

The protocol should indicate if you plan to explore between study variability, when detected, through subgroup or sensitivity analyses.

Clearly define which covariates will be used for subgroup analyses.

Report any planned sensitivity analyses, for example investigating small studies, studies with high risk of bias or industry sponsored studies.

📄 **Example subgroup analyses**

We will use subgroup analyses to explore possible sources of heterogeneity, based on the following:

- Vitamin C dosage (500 mg, 1000 mg, >1000 mg)
- Sex (Male, Female)

📄 **Example sensitivity analyses**

We will perform sensitivity analyses to explore possible sources of heterogeneity as follows:

- Risk of bias (by omitting studies that are judged as being high risk of bias)

How to handle data that can not be quantitatively synthesised

Most reviews have a narrative (qualitative) component that provides a textual or tabulated summary of the evidence. As you plan the analyses, it may become apparent that it will not be possible, or feasible, to combine data quantitatively. In these circumstances, the protocol should outline how the results will be reported in a narrative format.

💡 **Tip**

If you are unsure which effect measure or statistical method or model to use then consider seeking statistical advice.

Useful resources

Cochrane Handbook Chapter 10: Analysing data and undertaking meta-analyses

Risk of bias in individual studies

The assessment of risk of bias of the included studies is an important part of a systematic review. This evaluation contributes to the certainty or strength of the evidence if you are going to measure this (not all reviews will include this assessment). The methodological characteristics of studies at high risk of bias, such as inadequate allocation concealment for randomised trials, are more likely to result in an exaggeration of treatment effect compared with trials with adequate allocation concealment.

Risk of bias assessment

Risk of bias assessment is the process of evaluating the design and conduct of the individual studies included in the systematic review. It aims to identify potential sources of systematic errors in the design, conduct, or analysis of each study. It is useful to include information to support risk of bias assessment decisions when extracting data.

The goal of risk of bias assessment is to determine how well each study's results can be trusted. This assessment often involves evaluating the study's methodology, such as randomisation, blinding, handling of missing data, and other factors that could impact the validity of the results. It is important that the protocol states the criteria for risk of bias assessment.

Common tools include:

- Cochrane Risk of Bias Tool (RoB 2 and RoB 1) for intervention studies.
- ROBINS-I for non-randomised studies of interventions.
- Newcastle-Ottawa Scale for observational studies.
- Critical Appraisal Skills Program (CASP) checklist.
- QUADAS-C tool | Cochrane Methods within systematic reviews of diagnostic test accuracy
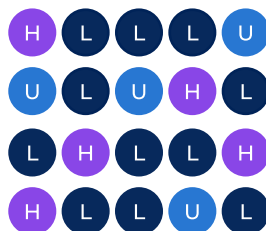
Evaluating the quality of
individual studies
(as high, low or unclear)

The protocol should describe which tool will be used to assess risk of bias. Provide a clear rationale if risk of bias will not be assessed in the review.

If you plan to use your own tool then a strong rationale should be provided for not using a previously validated/reliable tool.

Blinding of risk of bias assessors

In the protocol, describe who will assess risk of bias. Include details on the number of reviewers and any procedures for resolving conflict/s. Indicate if assessment will be independent and/or blinded.

Sensitivity analysis

Describe if there is a plan to utilise risk of bias assessment during analysis for sensitivity analysis or to restrict analyses to only low risk of bias studies. You may want to investigate if there are differences between treatment effects in studies with low risk of bias compared with those with high risk of bias.

📄 Examples

Randomised trials: We will use the Cochrane Risk of Bias Tool V1 for the assessment of risk of bias in each study. This includes an assessment of sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. A judgement of 'High risk', 'Low risk', or 'Unclear risk' will be made for each domain. These judgements will be made by two independent (blinded) reviewers, with a third reviewer for arbitration where conflicts cannot be resolved.

Non-randomised studies: We will assess the methodological quality of non-randomised studies (case-control and cohort studies) using the Newcastle-Ottawa scale. Scoring will be undertaken by two independent (blinded) reviewers with a third reviewer for arbitration where conflicts cannot be resolved.

Meta-bias(es)

Meta-biases affect the review as a whole rather than biases within individual studies and can influence the overall conclusions drawn from the systematic review. The protocol should indicate how these biases will be detected and handled, if they are present.

The most common meta-biases include:

Publication bias: Publication bias can arise when studies with positive results are more likely to be published than those with negative results or when small studies have different effect size estimates from larger studies. Assessment of publication bias is often represented visually by a funnel plot or assessed statistically with methods such as the Egger's test.

📄 **Example**

We will use a funnel plot to visually explore publication bias. In the presence of asymmetry, we will investigate possible explanatory factors including possible missing studies and study quality.

Selective reporting bias: Selective reporting bias in the included studies refers to when individual studies selectively report certain outcomes, often those with significant or positive results while omitting others. Significant results are more likely to be reported compared with non-significant results which can introduce misleading findings in the review. Reporting bias in the review itself occurs when the review authors selectively report or emphasise specific outcomes from the included studies. This can mislead readers about the overall findings of the review. Both types of bias affect the reliability and completeness of the evidence presented in the review. The review protocol provides transparency for planned and actual reporting and prevents selective inclusion of favourable data.

Sources of funding bias: Funding bias in reviews can come from financial support for the included studies or the review itself, potentially skewing results to favour the funder. The protocol should indicate that details on study sponsorship or funding will be sought for included studies. This maintains the review's objectivity and integrity.

📄 **Example**

This review was funded by a departmental research grant of $8000 from Covidence University.

Certainty of evidence

The protocol should describe any assessment used to judge the certainty (sometimes known as confidence or strength of evidence) in the body of the evidence in the review; how many reviewers will make the judgement, and if the judgements will be undertaken independently, or not.

For each outcome, the assessment should include risk of bias across all included studies based on:

- Inconsistency
- Imprecision
- Indirectness
- Publication bias
- Other factors (e.g. large effect size, dose effect relations)

This may increase or decrease the certainty in a summary statistic or treatment effect. The certainty of evidence is usually presented in a Summary of Findings table.

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

GRADE is widely recommended as the tool of choice for summarising the certainty of evidence and is used by Cochrane. Although the assessment is a judgement, GRADE provides a transparent framework to categorise the certainty of evidence as 'high', 'moderate', 'low' or 'very low'.

The protocol should identify up to seven important outcomes. The protocol should specify if the certainty of evidence will include studies that were not included in the meta-analysis.

The protocol should also state if certainty of evidence will not be evaluated and provide a rationale.


📄 **Example**

We will judge the quality of the body of the evidence for key outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The following domains will be assessed: risk of bias, consistency, directness, precision and publication bias. Judgements will include high, moderate, low and very low.

Figures and tables to include in an intervention systematic review

Including the right figures is crucial for effectively summarising and presenting your systematic review findings. The protocol should specify which figures will be included, where appropriate.

Here are some key figures that could consider including:

PRISMA figure: The PRISMA figure is a flow diagram that illustrates the process of study selection in a systematic review. The figure shows the number of records identified, excluded before screening (e.g. duplicates), included, and excluded at title and abstract screening, and full text screening. The figure is accompanied with reasons for exclusions at full-text review. Some teams also include reasons for exclusion after title and abstract screening. Sources (databases, registries, other sources) for the records identified can also be included for transparency.
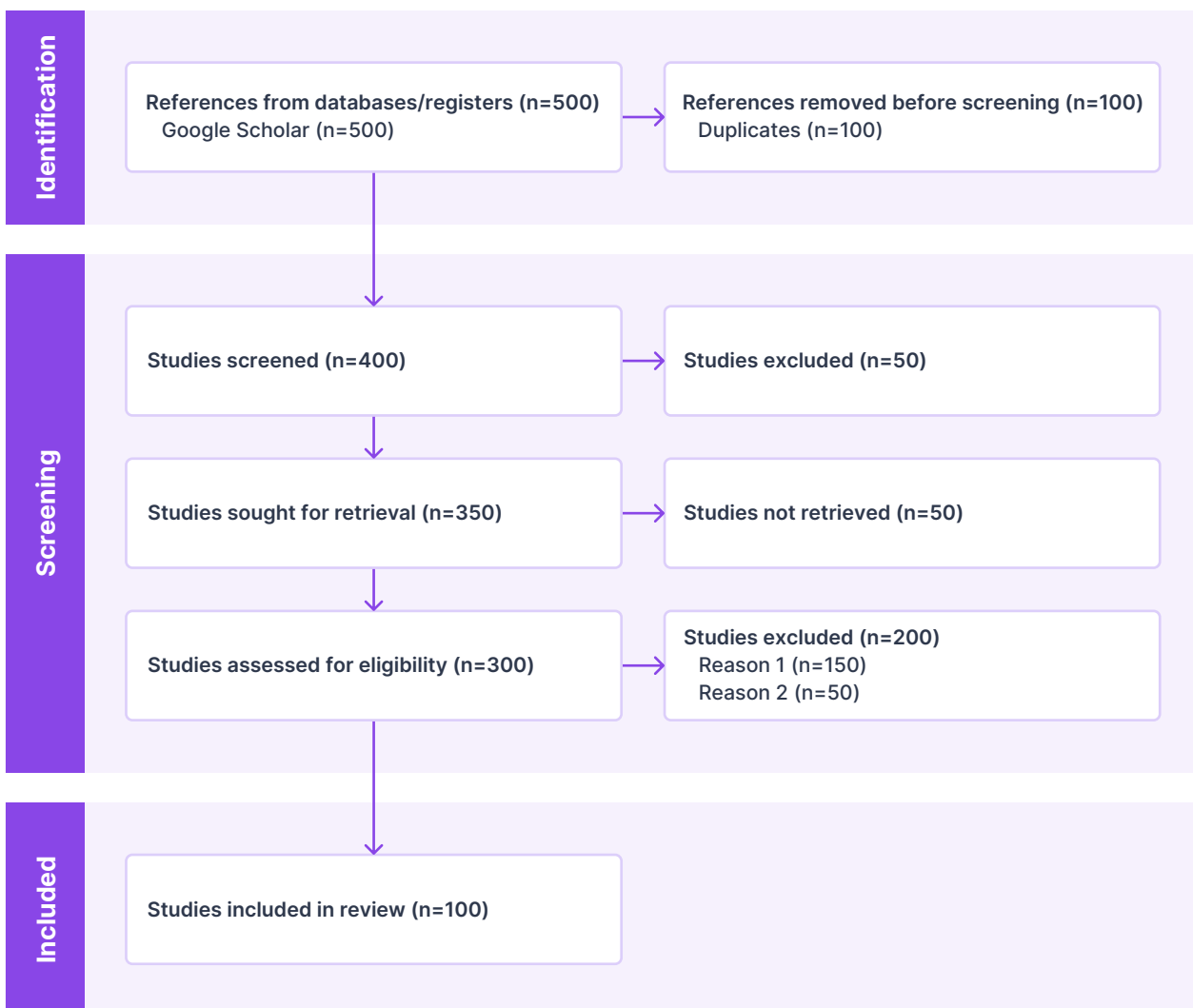
Risk of bias summary and graph: If you plan on conducting a risk of bias assessment of the included studies in your review, you should specify how you plan to present that information. You might want to tabulate it or use a graphical representation as illustrated below.
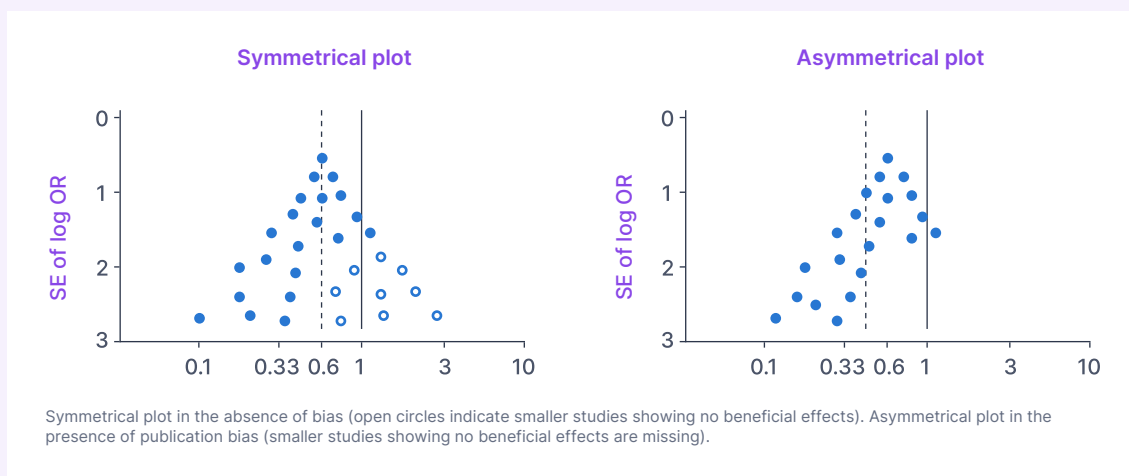
Forest Plots: Forest plots are required if you plan to conduct meta-analyses. They illustrate both the effect sizes from individual studies and the overall summary estimate (treatment effect). Forest plots help to identify heterogeneity.

Study	Vitamin C n / N	Placebo n / N	Weight	Risk Ratio 95% CI	Vitamin C vs Placebo Risk Ratio
Study 1	8 / 16	12 / 15	20.4%	0.63 (0.36, 1.08)	
Study 2	20 / 35	30 / 40	54.3%	0.76 (0.54, 1.07)	
Study 3	10 / 20	15 / 19	25.2%	0.63 (0.39, 1.04)	
Total	**38 / 71**	**57 / 74**	**100%**	**0.70 (0.54, 0.90)**	

Heterogeneity: Chi² = 0.56, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)
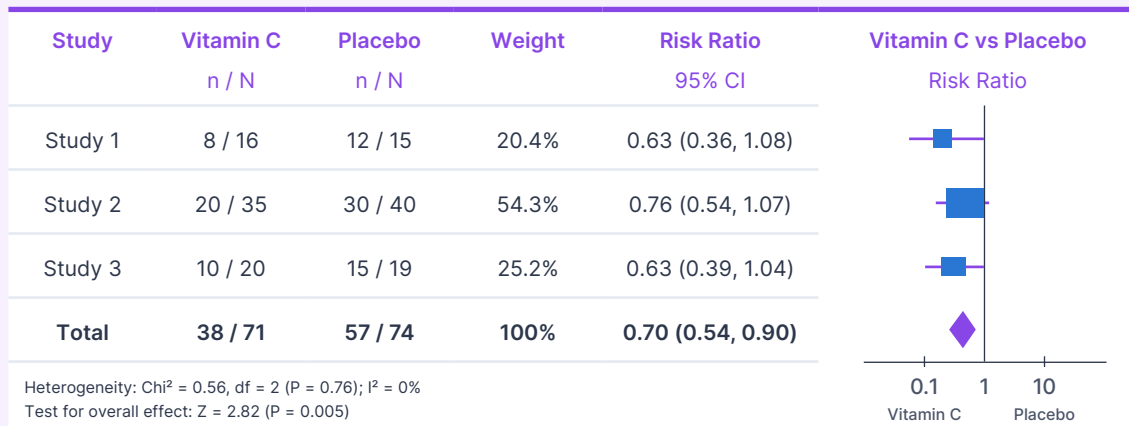
Funnel Plot: The funnel plot can be used to assess publication bias in meta-analyses. It plots the effect size against the standard error (or other measures of study precision) to visualize any potential asymmetry, which may indicate bias. Publication bias can arise when small negative studies are not published or may be due to low methodological quality in smaller studies. This would be represented by asymmetry in the funnel plot.

Symmetrical plot in the absence of bias (open circles indicate smaller studies showing no beneficial effects). Asymmetrical plot in the presence of publication bias (smaller studies showing no beneficial effects are missing).

Tables: The protocol should indicate which, if any, tables will be used to summarise the studies. Systematic reviews commonly include tables for

- characteristics of included studies
- characteristics of studies awaiting classification
- characteristics of ongoing studies.

Included studies: The characteristics of included studies are often summarised in a table. These tables provide clarification that the studies have met the eligibility criteria of the review.

📄 **Example table of 'Characteristics of included studies'**

Author	
Study Name	
Methods	
Participants	
Interventions	
Outcomes	
Notes	

Studies 'awaiting classification': Studies 'awaiting classification' includes potentially eligible studies that cannot be assessed for inclusion or exclusion in a systematic review due to insufficient or ambiguous information. These studies may impact your review findings and should not be included or excluded without further investigation. It is good practice to describe the study details in the 'Characteristics of studies awaiting classification' table, and to mention those that have the potential to influence the results.

📄 **Example table of 'Characteristics of studies awaiting classification'**

Study ID	
Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ongoing studies: It is important to identify ongoing studies, so that when a review is updated these can be assessed for possible inclusion. Even when studies are completed, some are never published which can increase the risk of bias in your review. Information about possibly relevant ongoing studies should be included in the review in the 'Characteristics of ongoing studies' table.

📄 **Example table of 'characteristics of ongoing studies'**

Study Name	
Trial registry number	
Methods	
Participants	
Interventions	
Outcomes	
Estimated sample size	
Start date	
Anticipated end date	
Authors contact information	
Notes	

📄 Examples

Example 1: We will use a PRISMA figure to detail the flow of records through the systematic review. We will include details of sources of records and reasons for exclusion at full text review. We will summarise how many studies were available for qualitative (narrative) and quantitative (meta-analysis) analysis.

Example 2: We will illustrate the risk of bias domains for each study in a Summary figure generated by the Robvis visualisation tool: https://sites.google.com/site/riskofbiastool/welcome/robvis-visualization-tool?authuser=0

Example 3: Where there are sufficient data to conduct meta-analyses, we will illustrate the findings for the primary outcomes and subgroup and sensitivity analyses using forest plots

Example 4: We will summarise the characteristics of included studies (Methods, participants, interventions, outcomes and notes), studies awaiting classification, and ongoing studies in tables.

06

Protocol amendments and deviations

Protocol deviations and amendments

It is fairly common to make changes to the systematic review protocol. You may realise that a search strategy needs to be updated or there is an outcome or a subgroup that the review team wants to include. Changes to reviewers or roles and responsibilities should also be updated. It's fine to make these changes as long as a clear rationale is provided. The main protocol registries (PROSPERO, INPLASY, Open Science Framework, Research Registry) allow you to amend or update registered protocols. However, making amendments after completion of data extraction is a potential source of bias and should be avoided where possible.

📖 **PRISMA for systematic review protocols (PRISMA P) - Item 4**

If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments

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To make an amendment to a protocol requires:

- **Clear rationale:** Clearly state the reasons for amending the protocol. There could be new evidence, changes in the research question, or modifications in the methodology. It is insufficient to state that the reason for an amendment was based on the request of a co-reviewer or a supervisor.

- **Documentation:** Keep an accurate record of all changes made to the protocol, including date of amendment and rationale. This is key for transparency and accountability.

- **Communication:** If the protocol has been registered with a protocol registry, such as PROSPERO, update the registration with the amended protocol to maintain transparency and avoid duplication. Decisions to make amendments should be agreed by the review team.

Amendments can be documented in a paragraph, supplement or tabulated (see example).

💡 Tips

- Deviations in the middle of the review process, that require a protocol amendment, can often be avoided by piloting search strategies, screening processes and data extraction templates in advance.

- Where possible, remember to update submissions to protocol registers with any amendments.

- Remember to update team members and changes to roles and responsibilities

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📄 Example protocol amendment table

Date	Protocol section	Original text	Amended text	Rationale
Date amendment was made	Section of the protocol updated e.g. outcomes	Relevant original text of the protocol	Change to the protocol text based on the amendment	Justification for amendment with a clear rationale

07

Top 5 tips for intervention systematic review protocols

Key takeaways

In this eBook we have shared the knowledge we have gained through our internal systematic review experts, our community of users, best practice content from Cochrane and PRISMA. Here are our top 5 tips for intervention systematic review protocols.

💡 **Top 5 tips for intervention systematic review protocols**

1. **Prepare before you start your systematic review.** Planning ahead will ensure that your review processes will be efficient with fewer chances of discrepancies and reduced risk of bias. Your review will be transparent and reproducible. Don't underestimate the length of time this process takes. A project plan like a Gantt chart can help you stay on track.

2. **Use a review framework** to create clear and well-defined eligibility criteria to guide the development of the search strategy and facilitate screening e.g. PICO.

3. **Use the protocol to guide the data extraction template.** A well thought-out protocol can be the skeleton for structuring the data extraction template. It will minimise the risk of selective reporting. It can also act as a roadmap for the review team and can reduce arbitrary decision making.

4. **Register your protocol** if you plan to publish the review findings and to avoid research wastage.

5. **Use the protocol as a framework to write up the final report.** A good protocol provides all the necessary background and methodological content for the final report or publication of the systematic review.

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