What is a systematic review?

A systematic review aims to provide a comprehensive, unbiased synthesis of many relevant studies in a single document using rigorous and transparent methods. It attempts to uncover all of the evidence relevant to a question in order to synthesize and summarize the existing knowledge on this specific topic. It is often the essential first step in the research process.

The quality of a systematic review depends on the extent to which methods are followed to minimize the risk of error and bias during the review process. The use of rigorous methods distinguishes systematic reviews from traditional literature reviews. As such, explicit and exhaustive reporting of the methods used in the synthesis is a necessity and a hallmark of any well conducted systematic review. A published systematic review is in a position to influence healthcare decisions and should be conducted with the same rigor expected of all research.

A Systematic Review therefore aims to be

- **Systematic** in its identification of literature
- **Clear and unambiguous** in its statement of objectives, materials and methods
- **Reproducible** in its methodology and conclusions

A systematic review

- Summarises the best available evidence
- Determines what is already known about your proposed research question
- Is useful to identify research gaps and priorities for generating new evidence to fill these gaps
- Is the highest level of the evidence hierarchy (NHMRC Level I)
- Can inform clinical practice guidelines
- Can be an ideal way to undertake and present background research for a PhD thesis
- May get published in a high impact journal
- Can get lots of citations

Planning for a systematic review

To conduct a systematic review, you must have a good basic knowledge of your review topic. It is essential to do some preliminary reading before you start the review process. This will allow you to make an informed judgment about whether a systematic review is feasible, useful and timely in your field of interest. For example, has a good systematic review already been published on your topic in the last 5-10 years? A good level of prior knowledge will also help you formulate a better review question.

Successfully managing a systematic review requires you to

- Work with a team – you cannot do a full good quality systematic review by yourself
- Communicate clearly with the team
- Be organised
- Be prepared for a considerable time commitment
- Set a timeline – it can take longer than anticipated
- Keep good records

The main steps in a systematic review are

1. Developing the protocol (including the review question)
2. Conducting the search
3. Screening search results (study inclusion/exclusion)
4. Extracting data
5. Assessing study quality
6. Synthesising the data (narrative and/or quantitative)
7. Evaluating the finding
8. Completing the manuscript

1. Developing your protocol

Registering your review

Researchers working on high quality systematic reviews will often register their protocols before commencing. Registering your title can be important to prevent duplication of effort with other researchers in your area. Some journals require you to have your protocol registered, but not all systematic reviews are registered.

You should check registration websites for reviews in progress before commencing your own systematic review. Sites where systematic review protocols can be registered include:

- PROSPERO - www.crd.york.ac.uk/prospero

The PRISMA Statement

- Preferred Reporting items for Systematic reviews and Meta-Analyses: The PRISMA Statement
- PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses, which is essential reading before starting a systematic review.
- Editors of journals increasingly expect systematic reviews to use PRISMA or similar guidelines.
- The PRISMA Checklist (http://www.prisma-statement.org/PRISMAStatement/Checklist.aspx) will guide you on how to develop a systematic review protocol and what to include in the manuscript.
Formulating your review question

Your review question must be clearly defined. What are you trying to find out?

A well-formulated question is the key to a high-quality systematic review. It should guide you in determining eligibility criteria, searching effectively for studies, collecting data from included studies and presenting findings for a systematic review. Your question must be answerable. If your question is too broad, your search will yield more information than you can possibly look through.

- *** Make sure that your question has not already been systematically reviewed ***
- For starters, you can search in the Database of Abstracts of Reviews of Effects (DARE): and/or in the discipline specific databases to check whether the question has already been registered as an ongoing review or answered in the published literature.
- Your review question should clearly identify all applicable components of the PICOS Statement:
  - Participants: disease/condition, age, gender, etc.
  - Intervention: treatment or exposure
  - Comparator or control: standard therapy, placebo, other
  - Outcomes: what the researchers are trying to measure, improve, affect, accomplish? e.g. morbidity, blood glucose level, cure rate
  - Studies: study designs, e.g. RCTs

E.g. To assess the effects of [an intervention or comparison] for [a health problem] in [types of people and disease or problem and setting]’

The PICOS statement will also help you develop clear inclusion criteria for your review.

**PICOS Statement**

**Participants**
- Determine the most important characteristics that describe the study participants you are interested in.
- Are you interested in healthy participants or participants with a specific disease/condition?
- Decide on a clear definition for the disease/condition (e.g. patients with multiple sclerosis clinically diagnosed at least 5 years ago)
- Are there any types of people who should be excluded from the review (e.g. people with certain comorbidities)?
- Are there relevant demographic factors such as age, sex, ethnicity?

**Interventions and Comparators**
- Decide on your experimental interventions of interest
- Decide on your control/comparative interventions of interest
- Which specific variations of the interventions are to be included (e.g. dosage, duration, personnel who deliver it, etc.)?
- How will you handle trials where multiple interventions are combined?
Outcomes

- The **primary outcome** is the most important main outcome/s that can be used to reach a conclusion about the effects of the intervention (beneficial, adverse, no effect)
- **Secondary outcomes** are extra outcomes that can contribute to explaining the effects of the intervention (e.g. adverse effects of a drug)
- You will need to define the methods used to measure outcomes and the timing of outcome measurements when designing your review protocol.

Study types

- Consider which study design is most appropriate to answer your review question
- Most systematic reviews focus on Randomised Controlled Trials (RCTs)
- Decide whether you will include Non-randomised Controlled Trials
- In some fields there are too few published RCTs to conduct a review, RCTs are not ethical (e.g. in some studies on pregnant females) or other study designs are more appropriate (e.g. cohort studies, case-control studies, cross-sectional studies).
- It is acceptable to use more than one study design in a systematic review

2. Conducting your search

Conducting a systematic review requires you to systematically locate, appraise and synthesise evidence from scientific studies on a specific topic. Your search enables you to find the studies that meet your inclusion criteria. A good search strategy is essential for a good systematic review.

You will need to define which sources to search (scientific databases, grey literature), the search process you will use and how you will select studies for inclusion.

It is a good idea to consult with a librarian at this stage as they can help you develop a more effective search strategy. You can book a session with UC Liaison Librarians LibraryLiaison@canberra.edu.au, to discuss your review.

When you are conducting your searches, keep track of what you are doing by documenting your search process in enough detail to ensure that it can be repeated and reported correctly in the review.

Documentation of your search strategy should include:

- databases used
- date of search
- dates of coverage provided by each database
- search terms used
- total publications found
- number of duplicate publications removed
- number of relevant publications
- limits applied (e.g. English language)
No single database will index all scholarly literature, and there is overlap between databases. Different databases may use different subject headings to describe the same subject, so the same search terms will produce different results in different databases even when the database content is similar.

Possible sources to include in your search

- Key scientific databases: MEDLINE, EMBASE
- Abstract and citation index databases: PubMed, SCOPUS, Web of Science
- *Note: you need to be wary of PubMed as it includes content from PubMed Central, which now has been shown to have a number of junk/predatory publications included. MEDLINE forms the primary component of PubMed’s content, so you may prefer to search MEDLINE through a different database vendor instead (e.g. Ovid or EBSCOhost)*
- Subject specific databases: IPA (International Pharmaceutical Abstracts), CINAHL and AMED (Nursing and Allied health), PsycINFO (Psychology and psychiatry), Global Health (Public and international health), PEDro (Physiotherapy)
- Clinical trial databases: CENTRAL (Cochrane), ClinicalTrials.gov (US National Institutes of Health), ICTRP (the International Clinical Trials Registry Platform through WHO)
- Dissertation databases: ProQuest dissertations and theses full text
- Best practice guidelines
- Google Scholar (but note that searches in Google Scholar can be difficult as you are likely to get a high number of out-of-scope results)
- Reference list searches (e.g. of retrieved or included studies)

**Search terms**

Select specific search terms that you can use consistently across your chosen databases to search for publications to include in your review.

1. Identify the main concepts and keywords. Search for your main concepts first, then limit further as necessary to get a manageable number of results.
2. Use Boolean logic to express relationships between search terms. Boolean logic involves joining synonyms or associated concepts with "OR" to broaden the search (e.g. backache OR back pain, teenagers OR adolescents). Intersecting concepts are joined with "AND" (e.g. scabies AND treatment) to narrow the search.
3. Remember that each database has its own unique set of commands. Information about these will be on the database help pages. For example, nearly all databases use OR and AND in a similar fashion, but while many databases use the truncation symbol *, some use $. It is important to ensure you are using the correct commands for each database you search.
4. Be aware of differences in American, English and Australian spelling and terminology. Most databases use American spelling and terminology as preferred subject terms. However, it is important to search for all known English spelling variations of a word to avoid missing any results (e.g. randomised and randomized).
5. Use Truncation (putting * at the end of a word stem will search all forms of the word): disab* (disability, disabilities, disabled)

6. Use double quotation marks "...." to search for a phrase: "type 2 diabetes", “head lice”

7. Wildcard ? will search for any single letter in the space. e.g. wom?n will search women, woman, organi?ation will search organisation, organization.

8. In some databases, wildcard * can also be used where alternate spelling may contain an extra character. e.g. p*ediatric, will search paediatric or pediatric, behavio*r, will search behaviour or behavior.

9. You can permanently save your searches within each database once you have set up a personal log-in. To keep your searches up to date, you may find it useful to set up an auto-alert to notify you when new records are added that fit your search criteria.

**Search strategy**

Check the search strategies in published systematic reviews for guidance on how to develop your own. Cochrane systematic reviews are a good place to start as they include detailed methods and are tightly quality controlled.

Perfect your search strategy in one database before translating it to other databases. Check the results – are you getting relevant articles? Are you picking up articles you already know should be included? If not, why not?

**Steps to conducting your database searches**

1. Perfect your search strategy
2. Systematically run your searches in each of your selected databases
3. Import search records from each database into an EndNote library. Each database uses a different method for importing references into EndNote. You may need to select all records, or import multiple pages of records.
4. Ensure that you are importing the Abstracts as well as the Citation Information.
5. Delete record duplicates in Endnote using “Find Duplicates”
6. Keep track of record numbers before and after removal of duplicates
3. Screening your search results

After obtaining a set of records from your initial database searches, you need to screen these records to determine whether they match the inclusion criteria for your review. This screening is done in two stages:

1. **Title and Abstract screening**
   A quick screen of record titles and abstracts to eliminate ineligible studies

2. **Full text Screening**
   A detailed screen of the full text to confirm eligibility and include studies in the review

To perform record screening, you will need the study Inclusion Criteria that you developed earlier. It is best to have these listed in a short document that you can share with your review team. It is good practice to have at least 2 reviewers independently screen the same records to ensure minimal bias. It is important that the second reviewer codes the records without seeing the first reviewer’s decisions to maintain independence. In the initial Title and Abstract screening stage reviewers may want to err on the side of inclusion, as looking at the full text in the next stage can help to resolve difficult decisions.

There are two good ways to manage record screening and ensure that all decisions are clearly recorded.

1. **Using EndNote**
   - EndNote has functions that can help to manage and code your references
   - For a small number of records (<100), the entire screening process can be easily done in EndNote
   - Set up EndNote Groups to help code your records at each screening stage: Retrieve, Exclude, Unsure
   - More detail about how to use EndNote to set up Groups and screen systematic review records is available from these online sources:

1. For a large number of records (>100), it is much quicker and simpler to use a special systematic review screening tool. There are several of these available online:
   - **Covidence** ([www.covidence.org](http://www.covidence.org)) – a subscription only tool which provides multiple functions and one free review
   - **Rayyan** ([https://rayyan.qcri.org/welcome](https://rayyan.qcri.org/welcome)) – a free tool which greatly speeds up screening and selecting studies for a systematic review
**Title and Abstract screening**

**Title/Abstract screening in EndNote**

- Set up an EndNote Group labelled ‘Retrieve’ and another labelled ‘Exclude’
- For each record, read the title and abstract to decide whether it matches your inclusion criteria
- If you are not sure whether to include a record, add it to the ‘Retrieve’ group so you can use the full text to make your final decision. Alternatively, you may set up an ‘Unsure’ group to deal with the records where you are uncertain.
- Once you have screened all of your records, use the “Find Full Text” command in EndNote to automatically locate and attach full text pdfs of journal articles to your ‘Include’ EndNote records

**Title/Abstract screening in Rayyan**

- The Rayyan review screening program is fairly self-intuitive, but it is a good idea to start by watching the introductory video on YouTube (also available on their homepage).
- Import your EndNote file into Rayyan
- Before using Rayyan, all collaborators need to sign up for individual accounts.
- To create a new review, select "New review..." from the home screen.
- There is no limit on the number of reviews one can create.
- Only the creator of the review can invite collaborators and change the blind setting (Blind OFF/ON).
- Export your EndNote search results as an EndNote file (.enw) or other accepted file type (listed on Rayyan website).
- It is possible to add records to an existing Rayyan project. To do this, open the project, and then click on "New Search" in the top right-hand corner.
- You can invite colleagues by email to join you in the review by clicking the ‘Invite’ button.
- To make a decision on a particular article, select it and then click ‘include’ or ‘exclude’. If you select ‘exclude’, you can also select from a list of reasons for exclusions or add your own reason.

**Full text screening**

- Repeat the process from the Title/Abstract screening but this time use full text
- Use the “Find Full Text” command in EndNote to automatically locate and attach full text pdfs of journal articles to your EndNote records
- Assign each record as Include/Exclude
- For the records that are Excluded you also need to record the reason why (based on PICOS statement)
  - Participants, Intervention, Comparator, Outcome, Study type
  - Other reasons – e.g. record unavailable
- Use 2 independent reviewers at this step and any disagreements should be discussed to resolve or referred to a third reviewer.
- Rayyan does not currently offer a simple way of hiding articles that have been excluded after the title/abstract stage. To conduct Full-text screening in Rayyan, you will need to reimport your selected
records from the Title/Abstract screening as a new project. For details on how to do this, see this page on the McGill University Library website. You can then link article pdfs to each of the records which are available to all collaborators on the review.

The PRISMA Flow Diagram

A PRISMA flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions.

![PRISMA 2009 Flow Diagram](image)

Populate your PRISMA flow diagram with the correct numbers of records, duplicates and reasons for exclusion and then include it in the Results of your systematic review.

**Inter-rater agreement (Cohen’s kappa test)**

This is a statistical test which compares the inter-rater agreement between the first and second reviewer. It should be completed for both screening processes - Title/Abstract (Retrieve/Exclude) and Full text (Include/Exclude).

To calculate this statistic, you need to know

- How many records both reviewers included
- How many records both reviewers excluded
- How many records the 1st reviewer included and the 2nd excluded
- How many records the 2nd reviewer included but the 1st excluded

<table>
<thead>
<tr>
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<th>REVIEWER 2</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>REVIEWER 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Include</td>
<td>Include</td>
<td>Exclude</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Exclude</td>
<td>2</td>
<td>76</td>
</tr>
</tbody>
</table>

If you have kept track of this in EndNote (using Labels and Notes) or Rayyan, you can export your screening results into Excel. For a relatively low number of records, it is also possible to manually count the numbers.

Enter your screening results numbers into the calculator on one of the websites below to get your Kappa value and the ‘strength of agreement’.

- [https://idostatistics.com/cohen-kappa-free-calculator/](https://idostatistics.com/cohen-kappa-free-calculator/)
- [https://www.graphpad.com/quickcalcs/kappa1/](https://www.graphpad.com/quickcalcs/kappa1/)

The magnitude of the kappa coefficient represents the proportion of agreement between or within raters greater than that expected by chance. A kappa of 1.00 represents perfect agreement.
There are other adjusted versions of this statistic which may be more suitable for your review, such as the Prevalence Adjusted Bias Adjusted Kappa (PABAK). You may want to discuss this with your review team and supervisor.

4. Extracting the data

Now that you have selected your studies for inclusion, you need to extract data from each of these studies for analysis and to answer your review question. But what data needs to be extracted? This varies according to your research question and will relate to your protocol.

For example, Cochrane reviews require as a minimum

- Source data: e.g. citation and contact details
- Eligibility: Confirmed eligibility or reason for exclusion
- Methods: e.g. Study design, study duration, study methodology relating to bias
- Participants: e.g. number, setting, age, sex, diagnostic criteria, country

Other data you may find relevant to your review includes

- Intervention: e.g. number of groups, specific intervention for each (giving enough detail for replication)
- Outcomes: e.g. measurement time points, outcome definition, units of measurements
- Results: e.g. number of participants in each intervention group, sample size, missing participants, summary data
- Other: Funding source, authors conclusions, references to other relevant studies

You will need to develop a specific data extraction tool (a form or table to fill in) to make the data extraction process easier and more consistent. Be sure to trial your tool on a couple of studies so that you know it works well for your set of records and that you have all of the information you require. It is best to have 2 reviewers extract the data from each study because data is not consistently presented across all studies on the same topic, and it can be easy to miss or misinterpret information.

You can find examples of data extraction forms in published systematic reviews in your field or in the links below. These can be modified to suit your review.

Cochrane data extraction form

Joanna Briggs Institute data extraction form
5. Assessing study quality

Studies that have met the inclusion criteria should be subjected to a more refined critical appraisal for quality. All included studies should be assessed for quality/risk of bias.

- Standardised Critical Appraisal Tools are available
- It is standard to include your tool/results as an appendix to your protocol
- Read the instructions carefully if using a pre-existing tool to ensure it is used correctly
- 2 reviewers should complete this step
- Extract the study quality data using the same process as for data extraction – it may take less time to simultaneously extract study data for review analysis and data for quality assessment.
- Record the agreement level between reviewers as this is required for most journals publishing systematic reviews
- You may decide to remove studies from the review with low quality/high risk of bias

Generally, a critical appraisal will consider:

**Question** - Does this study address a clearly focused question?

**Methodological quality** - Did the study use valid methods to address this question? To what extent do the study design and conduct eliminate the potential for systematic error (bias)?

**Precision** – What is the likelihood of random errors? (Often depicted as the confidence interval)

**External validity** - Are these valid, important results applicable to my patient or population?

When reading the full text of each article identified for inclusion in the review as part of the Data Extraction process, apply a Critical Appraisal Tool to each study selected for inclusion. Choose the tool that best fits with the type of review you are conducting. These differ by the review focus and the study types you have included.

**Websites with lists of tools to consider for assessing study quality**

- Joanna Briggs Institute
  Find a range of appraisal tools. Includes case control studies, case reports, cohort studies, diagnostic test studies, economic evaluations, prevalence studies, quasi-experimental studies, randomized controlled trials, systematic reviews, text and opinion, and more.

- Best Evidence Topics

- AMSTAR summary of existing tools

- Duke University
• Critical Appraisal Skills Programme (CASP)
  https://casp-uk.net/casp-tools-checklists/
  Critical appraisal tools for Systematic Reviews, Randomised Controlled Trials, Cohort Studies, Case Control Studies.

• International Centre for Allied Health Evidence: Critical Appraisal Tools
  A list of suggested Critical Appraisal Tools curated by the University of South Australia’s International Centre for Allied Health Evidence

• Himmelfarb Health Sciences Library
  http://guides.himmelfarb.gwu.edu/c.php?g=27797&p=170451

**Example tools to assess quality of Randomised Controlled Trials**

• **Cochrane Risk of Bias tool (Cochrane RoB 2.0)**
  https://sites.google.com/site/riskofbiastool/
  Cochrane Handbook - Assessing risk of bias in included studies
  Cochrane risk of bias tool for randomised controlled trials. The site also contains a link to ROBINS-I, a tool to assess Risk Of Bias In Non-randomised Studies of Interventions.

• **JADAD scale** - Jadad quality assessment scale for rating Randomised Controlled Trials - permits a rank of the studies in the Systematic Review allowing a score to be calculated, based on quality. The higher the score, the higher the quality. The scale was introduced in the journal article Jadad, A., Moore, R., Carroll, D., Jenkinson, C., Reynolds, D., Gavaghan, D., & McQuay, H. (1996).

**Interpreting the results on risk of bias**

- Are there any sources of bias across your studies?
- If so, what are they?
- What impact might these have on the results?

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Interpretation</th>
<th>Across studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Plausible bias unlikely to seriously alter the results.</td>
<td>Most information is from studies at low risk of bias.</td>
</tr>
<tr>
<td>Unclear</td>
<td>Plausible bias that raises some doubt about the results.</td>
<td>Most information is from studies at low or unclear risk of bias.</td>
</tr>
<tr>
<td>High</td>
<td>Plausible bias that seriously weakens confidence in the results.</td>
<td>The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.</td>
</tr>
</tbody>
</table>
6. Synthesising your data

Arrange your data according to your review objective. The comparisons between the outcome results are the “effect”.

The data synthesis aims to answer 4 questions:

1. What is the direction of effect?
2. What is the size of effect?
3. Is the effect consistent across studies?
4. What is the strength of evidence for the effect?

Analyses may be narrative or quantitative – both still aim to answer these 4 questions

- Narrative: structured summary and discussion of the studies’ characteristics and findings
- Quantitative: includes statistical analysis (e.g. meta-analysis)

7. Completing your manuscript

- Like other scientific research papers, a systematic review manuscript usually contains the following sections: Abstract, Introduction, Methods, Results and Discussion/Conclusion
- Start writing your Introduction while doing your preliminary research on the topic
- Start writing your Methods while developing your protocol
- Start writing your Results after collating and analysing your extracted data
- Use the PRISMA guidelines
- Stick to your protocol and reference it if you have published it
- Check the Journal requirements for systematic reviews to ensure you meet their guidelines. These are normally found in the ‘Instructions for Authors’ section on the Journal’s homepage.

Relevant parts of a systematic review

<table>
<thead>
<tr>
<th>Part</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Title</td>
<td>Contains the study design, population under study, and the term systematic review or meta-analysis</td>
</tr>
<tr>
<td>Abstract</td>
<td>Includes introduction, objective of the study, databases (information sources), eligibility criteria, number of participants, interventions (treatment) provided, study details, results, limitations, conclusions, and registration number of the systematic review (for registered ones)</td>
</tr>
<tr>
<td>Introduction</td>
<td>Includes summary of the findings in the area, objective of the review, and statement regarding the necessity of review</td>
</tr>
<tr>
<td>Methods</td>
<td>Includes the protocol and registration, study design, search strategies, study selection (inclusion, and exclusion criteria), databases (information sources), data extraction and analysis process, risk of bias/quality assessments of the studies</td>
</tr>
<tr>
<td>Results</td>
<td>Includes the results of selected studies (PRISMA flow chart), summary table of individual studies(synthesis), and risk of bias/quality assessment (usually presented in a table or figure)</td>
</tr>
<tr>
<td>Discussion</td>
<td>Includes summary of evidence, interpretation of results, explanation on the main findings, and limitations (related to risk of bias, search restriction, and language restriction)</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Includes brief and balanced statement on findings of the review and the contribution of the review in helping future researches in the area;</td>
</tr>
</tbody>
</table>
If the conclusion is not drawn, a declaration statement including the reasons (e.g. insufficient number of reliable studies/reliabilities of available data) should be provided.

**Funding**
Includes a statement describing the role of funding source and role of funder in the study design, collection of data, analysis, interpretation of data, or writing of report, etc. in the systematic review.

**References**
List of all references used in the systematic review (referencing style depends on the journal of interest).

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**References**


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-The End-