REVEAL – prior evidence for new trials

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REVEAL – PrioR EVidencE for new triALs

Abstract

This guide is for clinical researchers who plan a new clinical trial and need to rapidly and systematically review the literature on prior trials. The results of such a review can be used to (1) identify and characterise evidence gaps that justify a new trial (e.g., insufficient evidence for a given patient population, intervention, comparator, or outcome; concerns about methodological quality; or imprecise effect estimates), (2) inform the research question and design of the new trial (e.g., outcome measurements, sample size calculation, and practical conduct), and (3) provide a clear scientific background and rationale in the trial protocol (as required by the SPIRIT reporting guideline for protocols of intervention trials).

The guide follows a stepwise process with two main parts:

- **Part A describes a systematic search for and quality assessment of existing relevant systematic reviews on the topic of the planned trial.** If a relevant, good-quality and up-to-date systematic review of previous trials answers the planned research question, no further trial is necessary. If the systematic review concludes that more evidence on the planned research question is needed, the new trial can be convincingly justified, and the available evidence can be used to inform the design and conduct of the new trial. If there is no relevant, good-quality and up-to-date systematic review, the researcher must continue with Part B.
- **Part B describes a systematic search for and quality assessment of relevant clinical trials on the topic.** If there are no trials or only those that are methodologically flawed, or if too few previous trials exist to answer the planned research question, the new trial can again be convincingly justified. Any available evidence from prior trials can be used to inform the design and conduct of the new trial.

This guide includes (1) a *detailed guidance document* (= the document that you are reading at the moment) listing for each step the essential and optional tasks with explanations and useful resources, and sections ("How to proceed from here?") with information on how to use the identified evidence with real examples from the literature, (2) a *structured report form* that takes researchers through the process step-by-step and provides a template to document all the relevant information needed to prepare respective sections of funding proposals or trial protocols for submission for ethics review, and (3) a *worked example* with a completed report form and sample text for a funding proposal or a trial protocol.

Introduction

Before embarking on a new clinical trial, it is essential for researchers to assess the existing evidence landscape: Has this particular research question been previously addressed, and is there convincing existing evidence on this question? Reviewing the literature when planning a new clinical trial not only prevents unnecessary and unethical repetition and complies with the evidence-based research approach. It also provides useful information for the design and conduct of a new trial.

This guidance is for you if you are planning a clinical trial and you do not have the resources or skills to carry out a full systematic review (SR) to inform your planned trial.

This guidance helps you conduct a swift literature review. The results of your review will enable you to:

- Determine the necessity of initiating a new clinical trial based on available evidence.
- Identify and characterize existing evidence gaps for a given patient population, intervention, comparator, or outcome (PICO); concerns about methodological quality/risk of bias, or imprecise effect estimates in the current literature to justify a new trial.
- Revise or refine the research question (PICO) of the planned trial based on available evidence.
- Choose outcome measures that may facilitate future evidence synthesis (meta-analysis) including the results of your new trial.
- Learn about minimal clinically important differences or typical standard deviations / event rates of outcomes relevant for sample size calculations for your new trial.
- Learn about difficulties others encountered when conducting similar trials in this field to optimise the execution of your new clinical trial.
- Fulfill the SPIRIT reporting guideline for trial protocols' requirement to describe the scientific background and rationale, including a summary of relevant trials (item 9a).

We acknowledge that for a convincing justification of a new trial there need to be not only identified evidence gaps, but the research question also needs to be relevant for patients, care givers, and clinicians. These user perspectives should be considered when designing a new trial and can be elicited through qualitative research or surveys gathering perspectives of users, or synthesis of such studies as recommended by the evidence-based research approach. Consider also the involvement of user representatives in the whole process of trial planning, conduct, and results dissemination to enhance trial implementation and applicability of trial results.

How to use this guide

Begin with the report form – it guides you through the whole literature review process. Simply download ↓ it and start filling it in.

Both the guide and the report form are structured in the same way (see also the *figure* on the next page): In **Part A**, you will be searching for **published systematic reviews (SRs)** first. This is faster than first searching for individual trials, and if you find one or more good-quality and up-to-date SRs on the topic of your planned trial, then you may not need **Part B** to search for **published, unpublished or ongoing individual trials**.

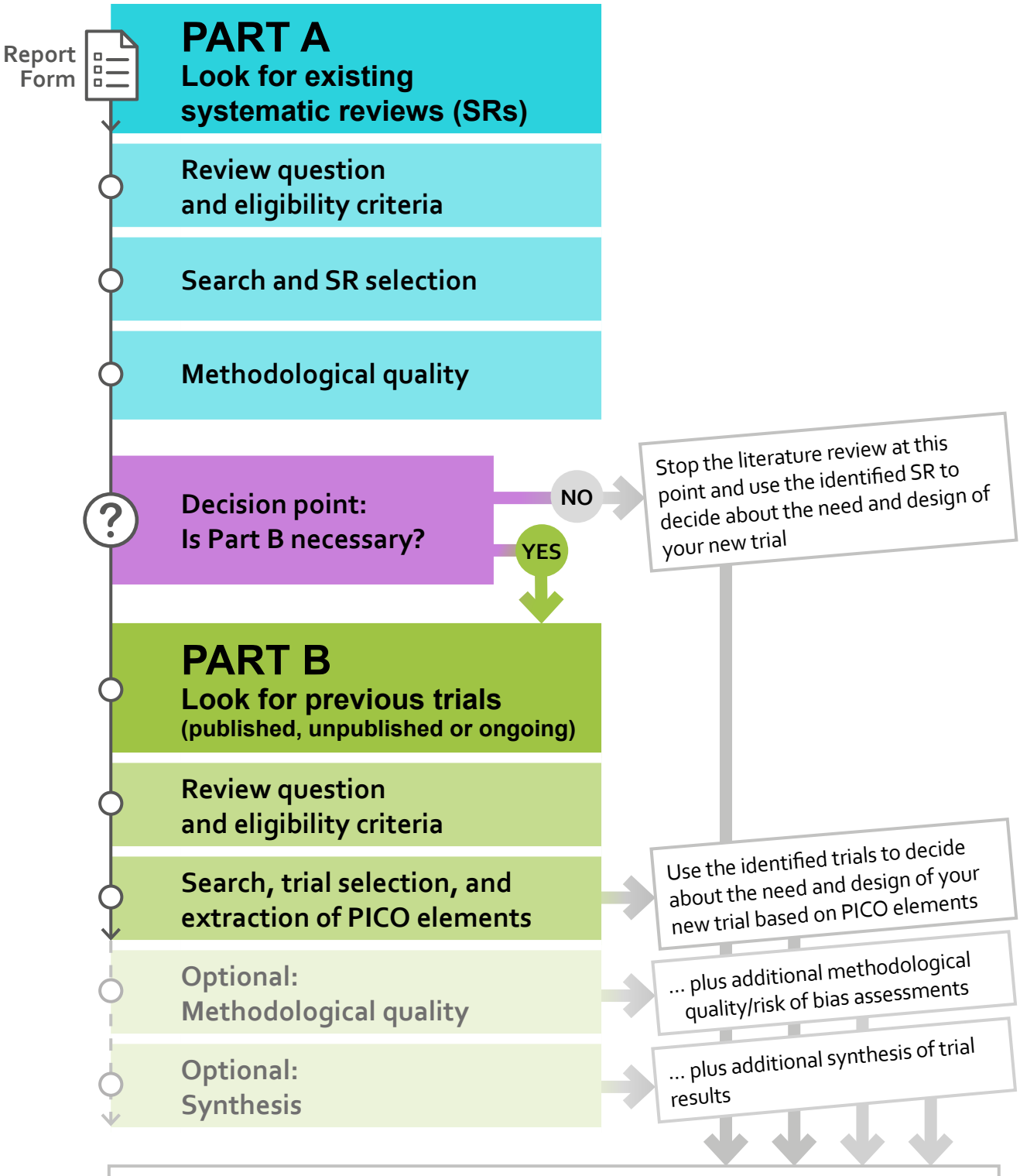
In both Parts A and B, we have defined **essential tasks** that you must carry out in your literature review. Additionally, we have added **optional tasks** that you can choose to do depending on your time and personnel resources. For each task we provide **further explanations** and **links to useful resources**. We have included the **"How to proceed from here"-sections** with information on how to use the identified evidence to decide in which instances a new trial is justified, illustrated by **real examples** from the literature.

Starting on page 7, you find a **navigation bar** at the bottom of each page. Click on it to move quickly from one part of the guide to another.

Disclaimer: The time to complete a swift literature review can vary substantially (several hours to several weeks) and depends on factors such as the topic of the research question, your knowledge and experience in systematic reviewing, and the available human resources, and support offered by your institution (e.g., library services, access to tools). Whatever your individual situation is, we strongly encourage you to follow the order of the listed essential tasks.

We acknowledge that the REVEAL guidance may contain terms that researchers with little prior exposure to systematic reviews and lay readers are not familiar with. Therefore, we recommend using a **glossary of commonly used terms in systematic reviews** to help with understanding the technical language used: Nagendrababu et al. 2020, https://doi.org/10.1111/iej.13217.

Overview of the swift literature review process



REVEAL output to be used to

- check for the need of a new trial and characterise possible evidence gaps based on
  - PICO-elements of previous trials
  - Risk of bias of previous trials
  - Imprecision of effect estimate in synthesis of previous trials
- inform the choice of outcome measures for a new trial
- learn about standard deviations/event rates of outcomes relevant for sample size calculations
- address item 9a of the SPIRIT guideline in the protocol of a new trial to provide an informative scientific background and rationale

Task overview and navigation

Click on the step for further explanations

PART A	Look for existing systematic reviews (SRs)
STEP A1: Review question	Conduct preliminary searches
	Structure review question using the population, intervention, comparator and outcome (PICO) framework
STEP A2: Eligibility criteria	Document inclusion and exclusion criteria for PICO elements
	Define additional elements in the eligibility criteria
STEP A3: Search	Use findings from preliminary searches to design search strategy
	Develop the search strategy with input from an information specialist
	Use at least two information sources to identify SRs
	Document searches
STEP A4: SR selection abstract level	Screen all identified titles/abstracts
	Refine eligibility criteria after screening 30–50 titles/abstracts
	Document the numbers of included and excluded titles/abstracts
STEP A5: SR selection full-text level	Retrieve full texts of all potentially eligible titles/abstracts
	Screen all full texts and record the main reason for excluding a reference
	Document the number of included and excluded full-text articles (with reasons for exclusion)
How to proceed from here?	You found eligible SRs: proceed to **STEP A6**
	You found no eligible SRs: proceed to **PART B**
STEP A6: Methodological quality of eligible SRs	Assess the methodological quality of eligible SRs
Decision point: Is PART B necessary?	NO, you found at least one recent and good-quality SR → stop the literature review at this point and use the identified SR to decide about the need and design of your new trial (see **Examples**)
	YES, you found an outdated good-quality SR → proceed to **PART B** and update the existing SR
	YES, you found no recent and good-quality SR → proceed to **PART B**

Task overview and navigation

Click on the step for further explanations

PART B	Look for previous trials (published, unpublished or ongoing)
STEP B1: Review question and eligibility criteria	Check whether the review question and eligibility criteria are still valid
	Specify (randomised) trials as eligible design
	For updates of good-quality SRs: restrict eligibility criteria regarding timeframe to after the SR's most recent search date
STEP B2: Search	Use findings from preliminary searches to design a search strategy
	Develop the search strategy with input from an information specialist
	Use at least two information sources to identify published trials
	Use ClinicalTrials.gov to identify ongoing or unpublished trials
	Document your searches
STEP B3: Trial selection abstract level	Screen all identified titles/abstracts
	Refine eligibility criteria after screening 30–50 titles/abstracts
	At minimum: search and screen the MEDLINE results directly in the platform (e.g., PubMed)
	At minimum: search and screen the ClinicalTrials.gov results directly in the platform
	Document the numbers of included and excluded titles/abstracts
STEP B4: Trial selection full-text level	Retrieve full texts of all potentially eligible titles/abstracts
	Screen all full texts and record the main reason for excluding a reference
	Review the whole entries of selected titles in Clinicaltrials.gov and record the main reason for excluding a reference
	Document the number of included and excluded full-text articles/trials register entries (with reasons for exclusion)
 **How to proceed from here?**	You found no published, unpublished or ongoing previous trials → stop the literature review and use the lack of evidence to justify your trial
	You found eligible published, unpublished or ongoing trials → proceed to **STEP B5**: Extract PICO elements of identified trials
STEP B5: Data extraction of PICO elements	Extract trial characteristics and the PICO elements for each identified trial
 **How to proceed from here?**	Option 1: Proceed to **STEP B6**: Assess the risk of bias of eligible trials
	Option 2 (with no further time and other resources): Stop the literature review and use the information on the PICO elements of identified trials to decide about the need and design of your new trial (see **Examples**).

PART A
Look for existing systematic reviews (SRs)

STEP A1 — Review question — Essential tasks

Conduct preliminary searches for existing SRs, trials, etc. to help define and refine your review question and eligibility criteria.

Preliminary searches are conducted during the preparation phase to get an idea of the available evidence on your topic.

For most people, this will mean 'Search as you usually do': Use information sources you are comfortable with (e.g., Google Scholar, PubMed) and browse through the results. You do not have to be systematic or comprehensive. It can be helpful to document the search terms you used.

Structure your review question using the population, intervention, comparator, outcome (PICO) framework.

The PICO framework works best for interventional research, but can also be applied to other types of questions (e.g., prognosis, diagnosis, aetiology).

For specific types of questions, you may need alternative frameworks (see resources for more information).

Resources:

University of Maryland, Framing a Research Question: https://lib.guides.umd.edu/SR/research_question

Evidence Based Library and Information Practice, Formulating the Evidence Based Practice Question: https://doi.org/10.18438/B8WS5N

STEP A1 — Review question — Optional tasks

Involve patients and clinicians in determining the review question and PICO elements.

Involving patients and clinicians can enhance clinical or public relevance and applicability. Perspectives and expertise from outside the research team adds valuable understanding of the individual topic.

Resources:

GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. https://doi.org/10.1136/bmj.j3453

Define the 3–5 most important outcomes.

Defining the most important outcomes often helps ensure a feasible review process; focus on the most patient-relevant outcomes and consider patient reported outcomes (PROs) which directly provide the patient perspective.

Resources:

Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. https://doi.org/10.1001/jama.2017.21903

Recommendations for including or reviewing patient reported outcome endpoints in grant applications. https://doi.org/10.1136/bmj.n1367

Search the COMET database for core outcome sets.

COMET provides core outcome measures in effectiveness trials. 'A core outcome set (COS) is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care'.

Resources:

COMET Initiative: https://www.comet-initiative.org/

STEP A2 Eligibility criteria — Essential tasks

Document your inclusion and exclusion criteria for the PICO elements of your review question.

Eligibility criteria (i.e., inclusion and exclusion criteria) add specific details to the PICO elements of your review question:

- e.g., population: age range, gender, disease stage/severity/duration
- e.g., intervention or comparison: the review question could state an entire drug class (e.g., serotonin-norepinephrine reuptake inhibitors), but in your eligibility criteria all drugs that are eligible are listed (e.g., Desvenlafaxine, Duloxetine, etc.)
- e.g., outcomes: specific outcome measures.

Detailed eligibility criteria are important because they will a) more accurately reflect the scope of the question, and b) help in making decisions during the literature screening process.

Eligibility criteria for SRs may be slightly different/broader than those for clinical trials (e.g., broader population).

Use the findings from your preliminary searches to help define your eligibility criteria.

Define any additional elements that are relevant for searching, study selection, data extraction or synthesis (e.g., eligible study designs, document types, languages, publication dates, full-text access).

Additional aspects may be important in deciding whether a SR is relevant for your literature review, e.g., the study designs the SR included, the publication date of the SR, etc.

STEP A3 Search — Essential tasks

Use the findings from your preliminary searches to design your search strategy (e.g., selection of search terms, relevant information sources).

Generally, you can base your search on two groups of search terms: a combination of a) alternative expressions for population AND b) alternative expressions for intervention. If the intervention is very new or the population is rare, you may need only one of these elements.

Searching for the comparator or outcomes is rarely appropriate: These elements are often less well reported in abstracts. Adding them to the search strategy might lead to missing relevant reviews.

Develop your search strategy with input from an information specialist (e.g., medical librarian).

Traditional systematic searches aim for the highest possible sensitivity: they aim to find all relevant publications and accept a large number of irrelevant documents in the search result as a trade-off. They often use many information sources, resulting in a large number of titles and abstracts to screen.

An information specialist can help you create searches with a higher specificity to find the majority of relevant studies but keep the number of hits manageable.

Resources:

Guidance for identifying SRs:

University of Tasmania, Systematic Reviews for Health: Finding Systematic Reviews: https://utas.libguides.com/SystematicReviews/Finding

JBI Manual for Evidence Synthesis, 10.2.6 Search Strategy for overviews of reviews (i.e., reviews of SRs): https://bit.ly/JBI-Manual

Use at least two information sources (including at least one bibliographic database, e.g., MEDLINE/PubMed) to identify SRs.

Systematic search sources can be separated into bibliographic databases (e.g., MEDLINE/PubMed, Epistemonikos, Cochrane Library) and additional sources (e.g., academic search engines, such as Google Scholar, or other supplementary search methods, such as checking the reference lists of included SRs). We recommend using at least one bibliographic database to ensure a high search sensitivity.

Some platforms (e.g., Epistemonikos, Cochrane Library) have reliable filter options for SRs. For other platforms/databases, you can use validated search filters to find SR: These are database-specific predefined search strategies whose performance has been tested (= validated).

Google Scholar usually retrieves a large number of records that are ordered by relevance. Because they cannot be easily exported in bulk, a pragmatic way to review them is to set Google Scholar to show 20 results per page and screen only the first page for every query. You can use the 'save' function to manually select references and export them into a reference management system.

Resources:

Find validated search filters, e.g., The ISSG Search Filter Resource: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home

The University of Rhode Island: Exporting Citations from Google Scholar: https://uri.libguides.com/google/gscholexport

Document your searches.

A detailed documentation of search strategies is helpful for the search section of Part B but also for search updates, e.g., when you write the manuscript of your own trial results: Record the date and names of the databases/search engines used, and copy and paste the exact search strings you used in each database/search engine.

Also, document any filters or limits you applied to your search, e.g., selecting only the first 20 records for every Google Scholar search result.

STEP A3 Search — Optional tasks

Use a reference management software (e.g., EndNote, Zotero, Mendeley, Citavi) or a SR support platform to collect search results and document the data selection process.

When using several search sources, you must expect overlap in the search results. You can import all your search results from each source into the reference management software and deduplicate the results. Alternatively, some supportive review platforms (e.g., Rayyan, SR Accelerator) also include deduplication functions.

Resources:

Guidance for search result deduplication:
Universität Bern, Removing duplicate records: https://ilias.unibe.ch/goto_ilias3_unibe_cat_2297227.html

Platforms with deduplication tools:
Rayyan: https://www.rayyan.ai/
The Systematic Review Accelerator (SRA): https://sr-accelerator.com/
Deduklick: https://www.risklick.ch/products/deduklick/

STEP A4 SR selection | abstract level — Essential tasks

Screen all identified titles and/or abstracts using your eligibility criteria to decide whether the SRs may be relevant.

There are several options to choose from for screening your search results from a database:

- Review the titles/abstracts directly online (e.g., collect them directly in PubMed)
- Download a csv/Excel file with the search results and document which references you included.
- Download the search results (e.g., as a RIS file); import it into a reference management software (e.g., Endnote, Zotero) to select eligible studies there.
- Upload the search results into supportive screening software (e.g., Rayyan, Covidence).

Supportive screening software can save resources through keyword highlighting, tagging functions and ranking the most relevant records with the use of artificial intelligence systems that aim to recognise prior inclusion or exclusion decisions.

Resources:

Examples for screening software:
Rayyan: https://www.rayyan.ai/
Covidence: https://www.covidence.org/
DistillerSR: https://www.distillersr.com/products/distillersr-systematic-review-software
Eppi Reviewer: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2914

Refine eligibility criteria after screening a first batch (e.g., 30–50 abstracts) and add further details for clarity, if necessary.

Often, during the study selection process, additional questions arise regarding the eligibility criteria details. Therefore, it is helpful to refine your eligibility criteria at the start of the screening process, after you screen a first batch. Refining can mean adding more detail for clarity or adding illustrative examples to make screening decisions easier.

Document the number of included and excluded abstracts using the PRISMA flowchart in the report form.

At the title/abstract level, it is not necessary to document the reasons for exclusion; it is enough to document the number of included and excluded abstracts.

STEP A5 SR selection | full-text level — Essential tasks

Retrieve the full texts of all potentially relevant abstracts.

There are several ways to retrieve the full texts of your potentially eligible references:

- Reference management software and screening software often provide a service to automatically retrieve full-text PDFs.
- Search using the DOI: you will be able to retrieve all open-access articles and those available to you through your institution.
- Search on Google Scholar: if the PDF is available to you, you will see a direct link.
- Check ResearchGate: authors often provide a download option of their article, or you can request a copy from the authors.
- Contact the corresponding author and ask for the full text.
- Ask a friend who works at another institution; they may have access to other publishers.

Screen all full texts using your eligibility criteria from STEP A2 to decide whether the SR is included and record the main reason for excluding a reference.

Reasons for excluding a full-text reference should be documented. The easiest way is to align the exclusion reasons with your eligibility criteria and number the exclusion reasons accordingly (e.g., X1_ineligible population).

Document the number of included and excluded full-text articles using the PRISMA flowchart in the report form and include the reasons for excluding for each full-text reference.

Screening software automatically keeps track of screening decisions and reasons for exclusion.

STEP A4+5 SR selection | abstract and full-text level — Optional tasks

Involve a second researcher (or more) and choose one of the following options:

- Mark unclear abstracts/full texts and discuss uncertain screening decisions with them.
- Use them to cross-check a subset of references: either a subset of abstracts/full texts (e.g., random 25%) or all excluded abstracts/full texts.
- Use them to screen all abstracts/full texts independently and discuss conflicting screening decisions.

Involving more researchers enhances the rigour and reliability of the review process, aiming at more accurate inclusion and exclusion of studies, reducing the risk of missing relevant studies. Different researchers may also bring varied expertise and perspectives into the research process.

If two or more researchers are involved:

- Conduct a screening pilot exercise with 30–50 abstracts (or 10% of retrieved records) and discuss uncertainties.
- Conduct a screening pilot exercise with 5–10 full texts (or 10%) and discuss uncertainties.

Screening pilot exercise: choose some records (e.g., 30–50 abstracts and 5–10 full texts), screen them independently and, afterwards, compare conflicting decisions. Justify the reasons for including versus excluding certain references and find consensus among the team. If the conflicts resulted from unclear eligibility criteria, consider refining the criteria. The aim of the pilot exercise is to get all involved researchers on the same page and discuss unclarities in the eligibility criteria.

How to proceed from here?

If you found **eligible SRs** after screening abstracts and full texts → proceed to **STEP A6**.

If you found **no eligible SRs** after screening abstracts and full texts → proceed to **PART B**.

STEP A6 — Methodological quality of eligible SRs — Essential tasks

Assess the quality of eligible SRs using a practical quality assessment tool (e.g., "fast and frugal" decision tree).

Only assess the quality of SRs that answer your review question. If you found many eligible SRs, only assess the quality of those most recent.

The "fast and frugal" decision tree allows an accelerated critical appraisal that is based on AMSTAR 2, a validated critical appraisal tool for SRs. However, if a more detailed appraisal is needed, you should consider using the full AMSTAR 2 assessment.

Resources:

"Fast and frugal" decision tree for the rapid critical appraisal of SRs: https://doi.org/10.1002/jrsm.1754

AMSTAR 2: https://amstar.ca/Amstar_Checklist.php

STEP A6 — Methodological quality — Optional tasks

Involve a second researcher (or more) and choose one of the following options:

- Use them to verify assessment of quality appraisal decisions.
- Use them to do the quality assessment of SRs independently.

If you involve a second researcher to verify your assessment decisions, highlight relevant paragraphs in the texts so that they can find the relevant content more easily.

Decision point – Is Part B necessary?

NO, if you found **at least one recent and good-quality SR** that addressed your review question → stop the literature review at this point and go to the next **How to proceed from here?** section.

Whether a SR can be considered '**recent**' or 'up-to-date' depends on the topic under investigation. In a fast-changing field, a SR with a search date of 2 years ago may be already out of date. In a field where developments are slower, a SR with a search date of, e.g., 5 years ago maybe still be usable; in particular, if a research question has been settled. As a rule of thumb, if you know already 1 or more RCTs not included in a SR due to an older search date, the SR should be considered 'outdated', but a SR with a search date of 1 year ago or less is typically considered 'recent'. In any case, we recommend consulting a content expert to judge whether the SR is outdated.

We consider a SR to be '**good-quality**' if it is useful for the purpose of REVEAL. To qualify as 'good-quality', a SR should meet the following criteria (based on reasoning from AMSTAR2 and the "fast and frugal" decision tree): The search covered at least 2 databases and a trial register, the search strategy was reported, the risk of bias of included trials was systematically assessed, and the results were synthesized qualitatively or quantitatively.

YES, if you found an **outdated good-quality SR** that addressed your review question → proceed to **PART B** and update the existing SR.

Update the SR: take the identified SR as a source of relevant trials and supplement it with a search for recent trials not covered by the outdated SR. You can use the search strategy of the outdated SR for the update.

YES, if you found **no recent and good-quality SR** → proceed to **PART B**.

If you did not find any SR or found only outdated or low-quality SRs on your review question, you should look for previous trials (PART B) to decide whether your trial is needed.

How to proceed from here?

Based on the identified recent and good-quality SR, you need to **decide whether your research question in its current form has been answered**, i.e. matching PICO, sufficiently precise evidence with low risk of bias.

> **Sufficiently precise evidence** means that the width of 95% confidence intervals around effect estimates is narrow enough to classify the result as relevant benefit (i.e. the limits of the 95% confidence interval make no effect or harmful effects implausible), or to classify the result as no relevant effect or even harmful effect (i.e. the limits of the 95% confidence interval make a relevant benefit implausible).

→ **If your research question has been answered,** your planned trial is no longer needed in its current form (see **Example 1**). Consider **modifying the research question (PICO) of your trial** if you are to proceed with it (see **Example 2**).

→ **If your research question has not been answered, characterize the evidence gap** in terms of PICO elements, methodological quality/risk of bias (see **Example 3**), or precision of effect estimates. SRs may already provide an analysis of potentially remaining evidence gaps (implications for further research; see **Example 4**).

In addition to using an existing SR for the characterisation of existing evidence gaps to justify your new trial, you should **make use of the SR evidence for the planning and design of your new trial**. This can be done by

(i) considering core outcome sets potentially used in the SR (or check the COMET database for existing core outcome sets https://www.comet-initiative.org/) when deciding about own trial outcomes,

(ii) using the SR to check for already established **minimally clinically important differences (MIDs)** (or check the PROMID database for already established MIDs, including patient-reported outcome measures, http://www.promid.org/) which are useful for sample size estimation and results interpretation of your own trial, and use the SR to check for typical standard deviations / control group event rates of outcomes relevant for sample size estimations (see **Example 5**), and

(iii) use the SR to potentially learn about difficulties others encountered when conducting similar trials.

PART B
Look for previous trials (published, unpublished or ongoing)

If you found an outdated SR on your review question or a SR that is on a similar topic but does not answer your review question, you can use the information from these SRs to inform your search for previous trials: e.g., to update an outdated SR, to choose relevant information sources or to specify eligible outcome measures.

STEP B1 Review question and eligibility criteria

Essential tasks

Check whether your review question and eligibility criteria from Part A are still valid and modify as necessary.

Eligibility criteria for SRs may be slightly different/broader than those for previous trials (e.g., broader population); therefore, it is important to check your criteria again at this stage and make changes as needed.

If in Part A, you identified outdated or low-quality SRs, you can still use these reviews to plan Part B, e.g., by specifying eligible population sub-groups, outcomes or outcome measures or study designs.

If you made major modifications, get feedback on the new versions of your review question and eligibility criteria, e.g., from another researcher, an experienced systematic reviewer or a clinical expert.

Specify (randomised) trials as eligible design.

Depending on your review question and your planned trial, you may, e.g., search for randomised controlled trials (RCTs) and exclude other study designs.

If you conduct an update of a good-quality SR that assessed your review question, restrict the eligibility for included published trials to those published after the SR's most recent search date.

If the good-quality SR searched the literature up until, e.g., 15 June 2022, then allow some overlap and set the search limits to start from June 2022 up to present.

STEP B2 Search

Essential tasks

Use the findings from your preliminary searches and Part A to design your search strategies for published, unpublished or ongoing trials (e.g., selection of search term, relevant information sources).

Generally, you can use the same elements (e.g., population and intervention) as identified in **STEP A3**. However, the information sources, search terms and study design filters may differ.

Develop your search strategies with input from an information specialist (e.g., medical librarian).

Search strategies to identify SRs are often broader than those aimed at identifying clinical trials. Therefore, it is likely that you will have to revise the search strategy you used for Part A to be more specific. Additionally, the bibliographic databases used for finding published trials use more sophisticated search functions than trials registers to find study protocols of ongoing trials: You must adapt your search strategy to the interface you use.

Resources:

Rapid reviews methods series: Guidance on literature search: https://doi.org/10.1136/bmjebm-2022-112079

Use at least two information sources to identify published trials:

1. Search in the bibliographic database MEDLINE (e.g., via PubMed).

2. Use one additional information source (e.g., Google Scholar, checking reference lists).

In most cases, MEDLINE (e.g., searched via PubMed) will contain the majority of relevant medical studies. Additional searches will help in finding trials not found by the search strategy or not available in MEDLINE.

Additional information sources:

- Use search engines, e.g., Google Scholar.
- Screen references of SRs found in Part A.
- Screen references of included trials.

Use ClinicalTrials.gov to identify ongoing or unpublished trials.

ClinicalTrials.gov is a US-based trials register widely used by international researchers. It mainly contains trial protocols but, in some cases, also results data. Searching it gives you an overview of ongoing research and completed but not (yet) published research.

Trials registers generally have very limited search functionalities, so searches must be simpler and broader than bibliographic database searches. Your search strategy should contain no more than two concepts (e.g., intervention, population) and only the most important search terms.

Resources:

Guidance for the systematic identification of ongoing or unpublished trials ('Searching clinical trials registers: guide for systematic reviewers'): https://doi.org/10.1136/bmj-2021-068791

Document your searches in bibliographic databases, trials registers and additional information sources.

Document your search steps while you conduct the searches, including:

- Names of all information sources used (e.g., databases, registers, search engines, reference list checking, etc.)
- Search dates for each information source
- Full search strategies for all databases, registers and websites, including any filters and limits used (e.g., study design filters, language and date limits, only exporting the first page of search engine results)
- Trials registers and websites: at minimum document the search terms and procedure that you employed (i.e. if you used combined searching and screening or if you used a reference management software).

STEP B2 Search — Optional tasks

Search two or more bibliographic databases and deduplicate the results before screening.

Using more than one database will increase the sensitivity of the search. Appropriate information sources depend on the topic, but also the relevant study designs.

If you are looking only for RCTs, the Cochrane Central Register of Controlled Trials (CENTRAL) is an appropriate second database in addition to MEDLINE/PubMed.

If you use a database other than CENTRAL, you can use validated search filters to find published trials, in particular if you are only interested in RCTs. If using filters built into search interfaces, you should understand how they function: depending on the database's default settings, not all the studies you are interested in may be found.

When using several search sources, you must expect overlap in the search results. You can import all your search results from each source and deduplicate the results. Alternatively, some supportive platforms (e.g., Rayyan, SR Accelerator) also include deduplication functions.

Resources:

Find information about databases for systematic searching: https://www.searchsmart.org/

Find validated search filters, e.g., The ISSG Search Filter Resource: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home You can browse by study design, but you should also check the 'Filters within database interfaces and machine learning classifiers' section.

Guidance for search result deduplication:
Universität Bern, Removing duplicate record: https://ilias.unibe.ch/goto_ilias3_unibe_cat_2297227.html

Platforms with deduplication tools:
Rayyan: https://www.rayyan.ai/
The Systematic Review Accelerator (SRA): https://sr-accelerator.com/
Deduklick: https://www.risklick.ch/products/deduklick/

Use additional trials registers to identify ongoing or unpublished trials.

Depending on your review question or the context of your planned trial, searching additional trials registers, e.g. national registers, may be useful.

- WHO International Clinical Trials Registry Platform (ICTRP) https://www.who.int/clinical-trials-registry-platform: Meta-registry that collects data from many national trials registers
- National trials registers, e.g., Australian New Zealand Clinical Trials Registry (https://www.anzctr.org.au), UK Clinical Study Registry (https://www.isrctn.com).

Export the search results in bulk and screen them separately from the search.

Search results from trials registers can usually be exported as tables or lists, but importing into reference management software and/or screening platforms may require additional steps. For a small search result, this may not be efficient.

Consider using Excel for screening the results of trials registers instead of other screening platforms where importing is required.

STEP B3 | Trial selection | abstract level — Essential tasks

Screen all identified titles/abstracts using your eligibility criteria from STEP B1 to decide whether the published trials are relevant:

- **Results from the search in bibliographic databases (e.g., MEDLINE/PubMed)**
- **Results from the search from additional information sources (e.g., Google Scholar, references of SRs found in PART A).**

There are several options to choose from for screening your search results from a database:

- Review the titles/abstracts directly online (e.g., collect them directly in PubMed).
- Download a csv/Excel file with the search result and document which references you included.
- Download the search result (e.g., as a RIS file); import it into a reference manager (e.g., Endnote, Zotero) to select eligible studies there.
- Upload the search results into supportive screening software (e.g., Rayyan, Covidence; see **STEP B3+4 | optional tasks**).

Refine eligibility criteria after screening a first batch (e.g., 30–50 abstracts), and add further details for clarity, if necessary.

Often, during the study selection process, additional questions arise regarding the eligibility criteria details. Therefore, it is helpful to refine your eligibility criteria at the start of the screening process, after you screen a first batch. Refining can mean adding more detail for clarity or adding illustrative examples to make screening decisions easier.

At minimum, search and screen the MEDLINE results and search engines directly in the platform (e.g., PubMed), i.e., through combined searching and screening, usually done by one person.

If you only search a single bibliographic database, you can screen the results directly on the platform you searched (e.g., PubMed). Read the abstracts in the results window and collect those that seem relevant in a marked list/Clipboard. Do not forget to document the number of initial retrieved records and the number of records you selected for full-text retrieval.

Screening of additional search sources depends on the method used: academic search engines usually have marked list and export functions; reference lists of publications can be checked manually in the full text or exported from a citation index.

If you search more than one information source that has an option for bulk exporting the search results, or if you work with a second screener, you should use a reference management software or a SR support platform (see **STEP B3+4 | optional tasks**).

At minimum, search and screen the ClinicalTrials.gov results directly in the platform, i.e., through combined searching and screening, usually done by one person.

Combining searching and screening usually involves a more 'Google-like' approach, which may be iterative:

- Type 1–2 simple search terms into the search field.
- Screen all identified records in the search results.
- Save any relevant trials, followed by another round of searching and screening if necessary.

Search results in trial registries, like ClinicalTrials.gov, are different from bibliographic databases, such as MEDLINE/ PubMed: there is no abstract and no full text in PDF format.

The search results page of ClinicalTrials.gov shows information about the study title, interventions and conditions. Use this information to screen for relevant trials within the register. In the first step of literature selection, screen the titles and in the second step, screen the complete entry.

Do not forget to document the number of initial retrieved records and the number of full records you screened.

If you search more than one trials register or work with a second screener, you should export the search results as a table or list or into a reference management software (see **STEP B3+4 | optional tasks**).

Document the number of included and excluded titles/abstracts using the PRISMA flowchart in the report form.

Document the total number of abstracts from MEDLINE/PubMed and titles from Clinicaltrials.gov that you screened and the number of included and excluded titles/abstracts.

At the title/abstract level, it is not necessary to document the reasons for exclusion; it is enough to document the number of included and excluded titles/abstracts.

STEP B4 Trial selection | full-text level — Essential tasks

Retrieve the full texts of all potentially relevant abstracts of published trials.

There are several ways to retrieve full texts of your potentially eligible references:

- Reference management software and screening software often provide a service to automatically retrieve full-text PDFs (of open-access articles).
- Search using the DOI: you will be able to retrieve all open-access articles and those available to you through your institution.
- Search on Google Scholar: if the PDF is available to you, you will see a direct link.
- Check on ResearchGate: authors often provide a download option of their article, or you can request a copy from the authors.
- Contact the corresponding author and ask for the full text.
- Ask a friend who works at another institution; they may have access to other publishers.

Screen all full texts using your eligibility criteria to decide whether to include the published trial. Record the main reason for excluding a reference.

Reasons for excluding a full-text reference should be documented. The easiest way is to align the exclusion reasons with your eligibility criteria and number the exclusion reasons accordingly (e.g., X1_ineligible population).

Review the whole entries of selected titles in Clinicaltrials.gov and decide whether the ongoing or unpublished trial is included. Record the main reason for excluding a reference.

Use the same reasons for excluding an ongoing or unpublished trial as for full texts of published trials. If further exclusion reasons are required, add them at this stage.

Document the number of included and excluded full-text articles/trials register entries using the PRISMA flowchart in the report form and include the reasons for excluding for each full-text reference.

Screening software automatically keeps track of screening decisions and reasons for exclusion.

STEP B3+4 Trial selection | abstract and full-text level — Optional tasks

Screen the results from two or more bibliographic databases using supportive screening software (e.g., Rayyan, Covidence).

If you use two or more bibliographic databases in your search, you should merge and deduplicate the results in a reference management software. Alternatively, some supportive screening software can also automate deduplication (see STEP A3 | optional tasks).

Supportive software can save resources through keyword highlighting, tagging functions and ranking the most relevant records with the use of artificial intelligence systems that aim to recognise prior inclusion or exclusion decisions.

Resources:

Examples for screening software:
Rayyan: https://www.rayyan.ai/
Covidence: https://www.covidence.org
DistillerSR: https://www.distillersr.com/products/distillersr-systematic-review-software
Eppi Reviewer: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2914

Involve a second researcher (or more) and choose one of the following options:

- Mark unclear abstracts/full texts and discuss uncertain screening decisions with them.
- Use them to cross-check a subset of references: either a subset of abstracts/full texts (e.g., random 25%) or all excluded abstracts/full texts.
- Use them to screen all abstracts/full texts independently and discuss conflicting screening decisions.

Involving more researchers enhances the rigour and reliability of the review process, aiming at more accurate inclusion and exclusion of studies, reducing the risk of missing relevant studies. Different researchers may also bring varied expertise and perspectives into the research process.

If two or more researchers are involved:

- Conduct a screening pilot exercise with 30–50 abstracts (or 10% of retrieved records) and discuss uncertainties.
- Conduct a screening pilot exercise with 5–10 full texts (or 10%) and discuss uncertainties.

Screening pilot exercise: choose some records (e.g., 30–50 abstracts and 5–10 full texts), screen them independently and, afterwards, compare conflicting decisions. Justify the reasons for including versus excluding certain references and find consensus among the team. If the conflicts resulted from unclear eligibility criteria, consider refining the criteria. The aim of the pilot exercise is to get all involved researchers on the same page and discuss unclarities in the eligibility criteria.

How to proceed from here?

If you found **no published, unpublished or ongoing trials** that fulfil your eligibility criteria → Stop the literature review and go on with planning your own trial: Use the fact that there are no similar published trials available as justification for your trial (see **Example 6**).

> Report the results from your literature review in the study protocol of your own clinical trial (see **Example 7**).

If you found **published or unpublished or ongoing trials** that fulfil your eligibility criteria → Proceed to **STEP B5**: Data extraction of PICO elements.

STEP B5 Data extraction of PICO elements — Essential tasks

Prepare a data extraction table with **the most important trial characteristics** and PICO elements.

> The data extraction table (often called data extraction form) usually contains the following **data items**: trial acronym or first author, publication year/trial status, publication reference or trial identifier from registry, country, setting, patient population (P), intervention (I), comparator (C), measured outcomes (O).

Extract data for **all identified trials** (published, unpublished, and ongoing).

> The table with trial characteristics and PICO elements helps you to identify similarities and differences between the identified trials, providing a clearer overview of 'what is known' and 'what remains unclear or missing' regarding the topic of interest (see **Example 8**).
>
> If you identified ongoing or unpublished trials, consider contacting respective trial investigators to clarify potentially missing information about such trials (e.g., premature discontinuation, anticipated completion, details about PICO elements).

STEP B5 Data extraction of PICO elements — Optional tasks

If your resources permit, involve a second researcher (or more):

- Conduct a pilot exercise with a small number of studies (1–3 studies) to test and refine the data extraction form.

Choose one of the following options:

- Use them to check data extractions of a subset of studies (e.g., random 25%).
- Use them to check data extractions of all studies to further minimise bias if resources permit.

> If you involve a second researcher who will check your data extractions, highlight relevant paragraphs in the texts so that they can find relevant content more easily.
>
> Consider using data extraction software. This could help provide examples for each item of interest, decrease the level of unnecessary extracted details and allow a consistent extraction among the team members.
>
> You could also use a spreadsheet and share it through a platform (e.g., MS Teams or Google Documents) so that everyone can edit it at the same time.

Resources:

Software to screen and extract data:

Covidence: https://www.covidence.org/
DistillerSR: https://www.distillersr.com/products/distillersr-systematic-review-software
Eppi Reviewer: https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2914

Software that aims to semi-automate data extraction:

Dextr: https://www.niehs.nih.gov/research/atniehs/labs/iha/dextr
RobotReviewer: https://www.robotreviewer.net/

How to proceed from here?

After you extracted the PICO elements of eligible published, unpublished, and ongoing trials, **check for evidence gaps** (see **Example 8**). You have now the following options:

→ **Option 1**: Proceed to **STEP B6**: Methodological quality/risk of bias assessment to further identify and more comprehensively characterize evidence gaps.

→ **Option 2** (with no further time and other resources): Stop the literature review here and **characterize identified evidence gaps** based on the PICO elements of eligible trials to justify your new trial (see **Example 8**) or, **if you cannot identify an evidence gap, consult with your team or supervisor** to decide whether the research question of your planned trial should be modified to close an evidence gap.

Report the methods and results from your literature review in the study protocol of your own clinical trial (see **Example 7**). Mention that you conducted a literature review using this guidance (and cite the guidance) and potentially add the completed report form with all documentations as an appendix to the study protocol for your planned trial or to a proposal.

STEP B6 Methodological quality/Risk of Bias (RoB) — Optional tasks

Assess the RoB of the included published trials using a rigorously developed and study design-specific assessment tool (e.g., ROBUST-RCT tool).

Use RoB ratings in SRs: If your included published trials are also part of a good-quality SR that you found, use the RoB assessments from the existing SR.

Study design-specific assessments means that the appropriate tool must be chosen for the type of study design. An RCT could be assessed by the ROBUST-RCT tool, while non-randomised studies must be assessed by other tools (e.g., ROBINS-I).

If you included a high number of published trials: Consider doing RoB assessments only for a subset (e.g., the 3–5 most recent or largest trials, or those with the highest relevance to your review question).

Assessing the potential risk of bias of included trials is always beneficial: Although it is complex, the questions in the ROBUST-RCT or the RoB 2 tool will help you gain an in-depth understanding of important steps you must consider when planning your own new clinical trial, which aims to be at the lowest RoB possible.

Resources:

ROBUST-RCT tool - manual: https://www.bmj.com/content/bmj/suppl/2025/03/25/bmj-2024-081199.DC1/wany081199.ww6.pdf

ROBUST-RCT tool - forms: https://www.bmj.com/content/bmj/suppl/2025/03/25/bmj-2024-081199.DC1/wany081199.ww4.pdf

RoB 2 Tool for RCTs: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2

ROBINS-I for observational studies (e.g., cohort studies): https://www.riskofbias.info/welcome/home/current-version-of-robins-i

If your resources permit, involve a second researcher (or more) and choose one of the following options:

- Use them to verify a subset of RoB ratings (e.g., random 25%).
- Use them to verify all RoB ratings and resolve conflicts by discussion.
- Use them to assess the RoB independently for all included studies and discuss conflicting assessments.

Involving more researchers enhances the reliability and may reduce bias in the critical appraisal of studies. Subjective judgement may influence a single reviewer's assessment. By involving a second researcher, different perspectives are considered and bias in judgement can be mitigated.

If you involve a second researcher to verify your assessment decisions, highlight relevant paragraphs in the texts so that they can find the relevant content more easily.

How to proceed from here?

Summarize in a table – in addition to the PICO elements from each trial – assessments of important RoB domains (e.g., random sequence generation, allocation concealment, blinding of patients, care-givers, and outcome assessors, and missing outcome data) and check for evidence gaps (see **Example 9**). You have now the following options:

→ **Option 1**: Proceed to **STEP B7** – Synthesis of trial results to additionally check for evidence gaps based on imprecision of effect estimates of important outcomes.

→ **Option 2** (with no further time and other resources): Stop the literature review here and characterize identified evidence gaps based on PICO elements and RoB assessment (RoB domains rated as high or unclear risk-of-bias for several trials) of eligible trials to justify your new trial (see **Example 9**). If you cannot identify an evidence gap based on PICO elements and RoB assessment (RoB domains mainly rated as low risk-of-bias), consult with your team or supervisor to decide whether the research question of your planned trial should be modified to close an existing evidence gap.

Report the results from your literature review in the study protocol of your clinical trial (see **Example 7**). You can use the information from identified trials, e.g., as a basis for sample size calculations (see **Example 5**) or to inform decisions on methodological aspects of your own clinical trial.

STEP B7 Synthesis — Optional tasks

Extract outcome data from eligible trials

Add outcome data (results) for the most important outcomes to your data extraction of trial characteristics (including PICO elements) and the RoB assessments to be able to synthesize the results and judge the potential benefits and harms of the intervention.

If you have updated an outdated SR, consider extracting the trial characteristics, outcome data, and the RoB assessments from the original SR for trials already included in the SR. Then add the information for the newer trials that you found with the search update.

Synthesise the results of eligible trials narratively and present the result in tables.

Presenting relevant data into tables makes it easier to identify similarities and differences between the included trials, providing a clearer overview of 'what is known' and 'what remains unclear or missing' regarding the topic of interest. It will also facilitate the narrative synthesis of the results.

Structure the synthesis in a way that is most useful to highlight the gaps in the evidence base, i.e., by outcome, by interventions or by comparisons (if you have multiple comparisons).

Resources:

The Synthesis Without Meta-analysis (SWiM) guideline provides further information on narrative synthesis: https://swim.sphsu.gla.ac.uk/

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If the data and your resources permit, consider performing a meta-analysis (MA) to synthesize the results of eligible trials quantitatively:

- Involve a researcher with statistical training in MA (e.g., statistician) to plan and conduct the MA, and decide which data and outcomes are appropriate.
- Use the findings from your MA to best inform the sample size calculation for your new clinical trial.

Establish whether MA is a valid option for all outcomes of interest, regarding the type of data (continuous versus dichotomous data), identified trials (population and study characteristics), and significance for your future steps. You can also choose the most relevant outcomes for your topic.

Resources:

Chapter on conducting MA in the Cochrane Handbook: https://training.cochrane.org/handbook/current/chapter-10

Software to conduct the MA: e.g., STATA, R, SAS, RevMan.

Assess the certainty of evidence for the most important outcomes, e.g., by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

- Involve a researcher with GRADE-training to assess the certainty of evidence.
- If possible, involve a second researcher to verify the correctness and plausibility of all ratings.

The overall strength of evidence for an effect can be graded. This approach enables the consideration of factors beyond study design and how they may influence recommendations for both practice and research. Assessing the certainty of evidence will help you to identify critical or important outcomes lacking sufficient data for conclusive judgments.

Resources:

Check the GRADEpro website for additional information related to certainty of evidence assessment: https://www.gradepro.org/

GRADE Training material: https://training.cochrane.org/introduction-grade

Assess the applicability of included trials' results and the purpose (pragmatic vs. explanatory) of your planned trial using the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS-2) tool.

An assessment of the purpose of previous trials can help you to better define the existing evidence gap.

The assessment of the purpose of your planned trial will help you to make design choices concordant with your trial's purpose.

Resources:

Information on PRECIS-2: https://www.precis-2.org/

How to proceed from here?

Congratulations! You have now conducted all the steps of a systematically conducted literature review.

Based on the summarized evidence from randomised trials, you need to decide whether your research question has been answered (i.e. matching PICO, sufficiently precise evidence with low risk of bias).

> Sufficiently precise evidence means that the width of 95% confidence intervals around effect estimates is narrow enough to classify the result as relevant benefit (i.e., the limits of the 95% confidence interval make no effect or harmful effects implausible), or to classify the result as no effect or harmful effect (i.e., the limits of the 95% confidence interval make a relevant benefit implausible).

→ **If your research question has been answered,** your planned trial is no longer needed in its current form (see **Example 1**). Consider modifying your research question (PICO) to close an existing evidence gap (see **Example 2**)

→ **If your research question has not been answered,** characterise the evidence gap in terms of PICO elements, low methodological quality/high risk of bias, or lacking precision of effect estimates for important outcomes (see **Examples 3**, **9**, **10**).

In addition to using an existing SR for the characterisation of existing evidence gaps to justify your new trial, you should **make use of the SR evidence for the planning and design of your new trial**. This can be done by

(i) considering **core outcome sets** potentially used in the SR (or check the COMET database for existing core outcome sets https://www.comet-initiative.org/) when deciding about own trial outcomes,

(ii) using the SR to check for already established minimally clinically important differences (MIDs) (or check the promid database for already established MIDs http://www.promid.org/) which are useful for sample size estimation and results interpretation of your own trial, and use the SR to check for typical standard deviations / control group event rates of outcomes relevant for sample size estimations (see **Example 5**), and

(iii) using the SR to potentially learn about difficulties others encountered when conducting similar trials.

> Report the methods and results from your literature review in the study protocol of your own clinical trial:
>
> - Mention that you conducted a literature review using this guidance (and cite the guidance) and briefly describe the methods of your literature review including your search strategy (see **Example 7**).
> - Report important characteristics of identified trials, RoB assessments, and important results with corresponding confidence intervals.
>
> **Optional:**
>
> Add the completed report form with all documentations as an appendix to the study protocol for your planned trial or to a proposal.
>
> Publish the findings of your literature review as a separate piece of research (e.g., in a preprint repository, peer-reviewed journal).

REVEAL
Real examples from the literature

The following examples illustrate how other trial investigators have used the results from previous systematic reviews (SRs) and/or prior trials to justify and inform the planning and conduct of their own trial.

Example 1 — The planned trial is no longer needed.

Examples from the literature show that many trials were conducted although the research question had already been answered creating research waste: The SRs by Fergusson et al. (1) and Ker et al. (2) showed that already several years before their publications, there was sufficient evidence answering the respective research questions.

(1) Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? Clin Trials 2005;2:218e29.

(2) Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.

Example 2 — Modifying the research question (PICO) to close an existing evidence gap.

The SR by Ker et al. 2012 (2) established tranexamic acid as effective treatment to reduce blood transfusions in surgical patients. The research team around Katharina Ker and Ian Roberts modified the research question to evaluate tranexamic acid in patients with acute gastrointestinal bleeding instead of surgical patients. They carried out a new SR on tranexamic acid versus placebo or usual care in patients with acute gastrointestinal bleeding (3) and found that previous trials were mostly of poor methodological quality (only one trial had adequate allocation concealment) and that only few trials provided data on potential adverse events such as thromboembolic events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism). By characterizing this uncertainty about the effectiveness and safety of tranexamic acid in patients with acute gastrointestinal bleeding, they justified their new trial in the protocol of the HALT-IT trial (4).

(2) Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.

(3) Manno D, Ker K, Roberts I. How effective is tranexamic acid for acute gastrointestinal bleeding? BMJ 2014;348:g1421

(4) Roberts I, Coats T, Edwards P, Gilmore I, Jairath V, Ker K, Manno D, Shakur H, Stanworth S, Veitch A. HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. Trials 2014;15:450.

Example 3 — Justifying a new trial based on an already existing SR.

The KIDS-STEP trial (5) examined adjunct corticosteroid therapy versus placebo in hospitalized children with community-acquired pneumonia. The investigators characterized the evidence gap in their trial protocol based on an already existing systematic review (6) as follows:

"The most recent Cochrane meta-analysis found evidence for a benefit from steroid treatment, but for children this was based on a small number of very heterogeneous and mostly unblinded trials aiming to investigate the efficacy of steroids in pneumonia with detection of specific pathogens, for example, Mycoplasma pneumoniae or respiratory syncytial virus (RSV).(6)"

(5) Kohns Vasconcelos M, et al. Randomised placebo- controlled multicentre effectiveness trial of adjunct betamethasone therapy in hospitalised children with community-acquired pneumonia: a trial protocol for the KIDS-STEP trial. BMJ Open 2020;10:e041937.

(6) Stern A, Skalsky K, Avni T, et al. Corticosteroids for pneumonia. Cochrane Database Syst Rev 2017;12:Cd007720.

Example 4 — SR providing an analysis of potentially remaining evidence gaps.

The systematic review by Picard & Tramer (7) on the analgesic efficacy of interventions to prevent pain from propofol injection noted with respect to recommendations for future research, that only limited data was available on children precluding any definitive conclusions in this population; and because the most efficacious analgesic intervention turned out to be a small intravenous dose of lidocaine, this should be used as comparator for future RCTs testing new interventions on this topic. However, they further point out that

"*The lidocaine-tourniquet method is undeniably effective and simple to perform. This begs the question as to the necessity of clinical studies that may identify yet another intervention with some analgesic efficacy to prevent pain on injection with propofol.*"

(7) Picard P, Tramer MR. Prevention of pain on injection with propofol: A quantitative systematic review. Anesth Analg 2000;90:963–9

Example 5 — Prior trials provide information relevant for sample size calculation.

The ESTREL trial (8) examined whether levodopa, in addition to standardized rehabilitation therapy, enhances the functional recovery (measured by the Fugl-Meyer-Motor Assessment [FMMA] total score) in patients with acute ischemic or hemorrhagic stroke compared to placebo. The investigators relied on prior evidence for their sample size calculation as follows (specific References not relevant for illustration):

"*Assuming, that the FMMA is normally distributed with a standard deviation of 25 points (as based on the FLAME-trial (Ref) data), 548 participants will allow to detect a mean difference between the levodopa- and the placebo-group in the FMMA total score of 6 points at 3 months (which we assumed to be patient-relevant based on prior research (Refs on minimal clinically important differences)) with a power of 80% (two-sided significance level of 5%).*"

(8) Zietz A et al. Enhancement of STroke REhabilitation with Levodopa (ESTREL): Rationale and design of a randomized placebo-controlled, double blind superiority trial. Eur Stroke J 2024;9(4):1093–1102

The OSPIC trial (9) investigated whether oral corticosteroids compared to placebo increase the cough-related quality of life assessed by the Leicester Cough Questionnaire (LCQ) score 14 days after randomization in adults with post-infectious cough. They described their sample size calculation as follows:

"*Sample size was estimated to have 80% power to detect the minimal clinically important difference (MCID) set at 1.3 points LCQ [Ref for MCID of LCQ]. To be able to detect an MCID of 1.3 points with a power of 80%, a total of 204 patients need to be recruited for both arms. … We expect a drop-out rate of 10%, similar to that in the trial by Wang et al. [Ref]. Sample size estimation was based on the assumption that individual LCQ scores are normally distributed. Raj et al. [Ref] reported a standard deviation (SD) of 3.3 points. A recent trial with a design and study population similar to ours reported a SD of 2.9 (Ref). We decided to use the more conservative assumption of 3.3 points.*"

(9) Merlo C et al. Oral corticosteroids for post-infectious cough in adults: study protocol for a double-blind randomized placebo-controlled trial in Swiss family practices (OSPIC trial). Trials 2020;21:949

Example 6 — Justification of a new trial based on lack of similar trials on a topic.

The LInezolid Plus Standard of care (LIPS) trial (10) evaluates combination antibiotic treatment with linezolid versus placebo for patients hospitalized with S. aureus bacteraemia. The investigators reported the following about their literature search in the protocol (publication in preparation):

"*Linezolid strongly reduced the expression of S. aureus virulence factors in preclinical studies,(Ref) making it an ideal candidate to use clinically. Expert opinion and some guidelines advocate this strategy for severe infections or for S. aureus strains with known toxin expression.(Refs) However, evidence from RCTs for this approach is still lacking: our systematic literature search for published or planned RCTs (in PubMed, Embase, and the Cochrane Central Register of Controlled Trials [indexing planned RCTs from clinicaltrials.gov and WHO ICTRP]) that was developed by an information specialist from the University Medical Library yielded 943 hits (search conducted in June 2023). None of those reported RCT results or an ongoing RCT involving an antibiotic combination treatment with linezolid for S. aureus bacteraemia.*"

(10) Registration in clinicaltrials.gov: Kühl et al. 2025. Combination Antibiotic Treatment With Linezolid for Staphylococcus Aureus Bacteraemia: A Randomised Controlled Trial (NCT06958835)

Example 7 — Reporting of literature review results in a trial protocol.

The CITrUS trial evaluated a single-dose versus 3-day cotrimoxazole prophylaxis in men with transurethral resection or greenlight laser vaporisation of the prostate. The investigators described their literature search for previous or ongoing trials in the protocol (additional file 1 in (11)) as follows:

"*In a systematic literature search in Medline (via PubMed, last search 20. March, 2018; detailed search strategy listed in the appendix '17.1 Search strategy'), we identified eight RCTs which assessed the efficacy of single-dose AP [Antimicrobial Prophylaxis] compared to prolonged AP.*"...

"*A search on the International Clinical Trials Registry Platform (ICTRP) from the WHO (last search 20. March, 2018) was conducted to assess if there are currently ongoing RCTs which assess the impact of a single-dose AP compared to a prolonged AP for TURP and GL. One RCT was identified (CTRI/2017/09/009721) which plans to evaluate the efficacy of one day amikacin compared to 3 days in patients undergoing TURP.*" ...

"*Appendix: 17.1 Search strategy*

("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR "antibiotic"[tiab] OR "antibiotics"[tiab] OR anti-bacterial agents[tiab] OR anti-bacterial agent[tiab] OR antibacterial agents[tiab] OR antibacterial agent[tiab] OR Bacteriocidal Agents[tiab] OR Bacteriocidal Agent[tiab] OR Bacteriocides[tiab] OR Bacteriocide[tiab]) AND (((Transurethral[tiab] OR greenlight[tiab] OR green light[tiab] OR laser[tiab] OR Photoselective vaporisation[tiab] OR Photoselective vaporization[tiab]) AND (prostate[tiab] OR "Prostate"[Mesh] OR Prostatectomy[tiab] OR "Prostatectomy"[Mesh] OR Prostatectomies[tiab])) OR "transurethral resection of prostate"[MeSH Terms] OR TURP[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti] NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))

Searched: 20. March 2018, PubMed; 117 Hits"

(11) Speich et al. Single-dose versus 3-day cotrimoxazole prophylaxis in transurethral resection or greenlight laser vaporisation of the prostate: study protocol for a multicentre randomised placebo controlled non-inferiority trial (CITrUS trial). Trials 2019;20:142

Example 8 — Presentation of extracted trial characteristics (PICO) in a table to identify similarities and differences.

A systematic search identified 6 RCTs assessing different treatments for patients with postinfectious cough in preparation for the OSPIC trial (oral corticosteroids vs placebo in adults with postinfectious cough on cough-related quality of life (12). The previous RCTs can be presented as follows:

Publication	Country	Number of pats	Cough duration	Number of pats with postinfect. cough	Intervention(s) and control	Primary outcome	Other outcomes
Wang et al. 2014 (ref)	UK	276	2–8 weeks	NR	Montelukast 10mg daily vs placebo	LCQ score (cough specific QoL) at 14 and 28 days	Overall cough severity Cough cessation Further interventions for cough Adverse events
Zanasi et al. 2014 (ref)	Italy	92	≥3 weeks and <4 weeks after URTI	92 (100%)	Salbutamol plus ipratropium bromide vs placebo	Cough severity at 10 and 20 days	Lung function Adverse events
Woodcock et al. 2010 (ref)	UK, Latin America, South Africa	91	≥2 weeks and <90 days after viral URTI	NR	N0P1 receptor agonist 100mg td vs codeine 30mg td vs placebo	Cough severity at 5 days	Cough frequency Sleepiness scores Patient diary Adverse events
Zolghadrasli et al. 2009 (ref)	Iran	100	>3 weeks	83 (83%)	Gelatine 5cc 3x/day vs previous antitussive medication	NR	Subjective assessment of improvement Adverse events
Ponsioen et al. 2005 (ref)	Netherlands	135	≥2 weeks	89 (67%)	Inhaled fluticasone td vs placebo	Cough score at 14 days	Cough score improvement >50% Days off work Lung function Patient diary Adverse events
Pornsuriyasak et al. 2005 (ref)	Thailand	30	>3 weeks	NR	Four puffs of budenoside td vs placebo	NR	Symptom score at 14 and 28 days Lung function

NR, not reported; URTI, upper respiratory tract infection; QoL, quality of life; LCQ, Leicester Cough Questionnaire

Inferences that can be made from the table:

- No RCT tested oral corticosteroids for postinfectious cough
- Only one RCT clearly focused on patients with postinfectious cough (Zanasi 2014)
- Large heterogeneity in countries, cough durations, interventions, and outcomes

(9) Merlo C et al. Oral corticosteroids for post-infectious cough in adults: study protocol for a double-blind randomized placebo-controlled trial in Swiss family practices (OSPIC trial). Trials 2020;21:949

Example 9

Presentation of extracted trial characteristics (PICO) together with important RoB domains in a table to identify similarities and differences.

The primary objective of the KIDS-STEP trial was to evaluate

"*whether treatment of children hospitalized for CAP [community acquired pneumonia] with oral betamethasone is superior to placebo in terms of the proportion of children reaching clinical stability (defined as ready for discharge or with normal vital signs) at 48 hours after hospitalization.*" (5)

Previous RCTs evaluating adjunct steroids in children with pneumonia including risk of bias assessment were the following:

Publication	Pat. population	Intervention and control	Outcomes	Sequence generat.	Allocation conceal-ment	Blinding of pats & personnel	Blinding of outcome assessors	Missing outcome data
Luo et al. 2014	58 children hospitalised with Mycoplas pneu, 1 centre in China	Prednisolone po, 5 days vs usual care	Hypoxia duration, Time to clin cure, Clinical failure, Adverse events	Unclear	Unclear	High risk	High risk	Low risk
Nagry et al. 2013	59 children hospitalised with CAP, 1 centre in Hungary	Methylprednis iv, 5 days vs placebo	Clin improve day 7, Time to clin cure, Clinical failure, Adverse events	Low risk	Unclear	High risk	High risk	Low risk
Van Woensel et al. 2003	85 children ventilated due to RSV pneumonia, 5 centres, Netherlands	Dexamethas iv, 2 days vs placebo	Ventilat duration, length ICU stay, Time to clin cure, length hosp stay	Low risk	Low risk	Low risk	Unclear	Low risk
Wu et al. 2014	108 children hospitalized with Mycoplas pneu, 1 centre in China	Dexamethas iv, then predni po, 7-10 days vs usual care	Clin improvement, Time to clin cure, Superinfections, Adverse events	Unclear	Unclear	High risk	Unclear	Low risk

CAP, community acquired pneumonia

Inferences that can be made from the table:

- Most RCTs focus on pneumonia with specific pathogens (Mycoplasma pneumoniae, RSV), not unselected children with community acquired pneumoniae
- Most trials were single-centre and included small number of children
- Large heterogeneity in patient populations, countries, and interventions
- With respect to planned primary outcome of KIDS-STEP (clinical stability/clinical cure), which is to some degree subjective, blinding of outcome assessment is important; however, previous trials had all high or unclear risk of bias for this dimension
- Except for Van Woensel 2003, methodological quality of previous RCTs was rather poor

(5) Kohns Vasconcelos M, et al. Randomised placebo- controlled multicentre effectiveness trial of adjunct betamethasone therapy in hospitalised children with community-acquired pneumonia: a trial protocol for the KIDS-STEP trial. BMJ Open 2020;10:e041937.

Example 10 — Characterizations of evidence gaps based on PICO elements, RoB assessments, and results of evidence synthesis.

Examples of well-reported justifications in protocols for a new trial based on evidence gaps in prior research:

HEMOTION trial

(12) Turgeon et al. Haemoglobin transfusion threshold in traumatic brain injury optimisation (HEMOTION): a multicentre, randomised, clinical trial protocol. BMJ Open 2022;12:e067117.

"*The evidence to support transfusion strategies in patients with TBI [traumatic brain injury] remains scarce. In a systematic review of studies in neurocritical care patients, we found insufficient evidence to support the use of a specific transfusion threshold to improve morbidity and mortality.(Ref) A recent randomised controlled trial showed no effect of red blood cell (RBC) transfusion on neurological outcomes in patients with moderate or severe TBI, although the expected effect size was large and most patients included were not anaemic.(Ref) To date, clinical practice guidelines are based on limited evidence and do not provide clear recommendations regarding RBC transfusion in TBI.(Refs) As a result, transfusion practices vary greatly within and between centres (Refs); many clinicians extrapolate the evidence supporting the non-inferiority of a restrictive strategy in critically ill patients without TBI (Refs) while others advocate for a liberal transfusion strategy pending stronger evidence to support this practice.(Ref)*"

DISTAL trial – EnDovascular therapy plus best medical treatment (BMT) versus BMT alone for MedIum VeSsel Occlusion sTroke: a prAgmatic, international, multicentre, randomized triaL

(13) Psychogios et al. Endovascular treatment for stroke due to occlusion of medium or distal vessels. N Engl J Med 2025;392:1374-84. – original protocol included as supplement

"*3.1 Research question and research in context*

The proposed study aims to assess if EVT [endovascular therapy] in addition to best medical treatment (BMT) reduces the degree of disability and dependency in daily activities 90 days after a MeVO [medium vessel occlusion] stroke compared to BMT alone.

3.2 Systematic review: Search strategy and results

We conducted a systematic review of the existing randomized trial evidence on mechanical thrombectomy in AIS [acute ischemic stroke] patients for the design and planning of the proposed trial. We included randomized controlled trials (RCTs) reporting on long-term disability or dependency (as measured with the modified Rankin Scale) in patients with AIS due to any cause (i.e. with or without MeVO). We searched Embase (via Elsevier), Medline (via Ovid), and the Cochrane Central Register of

Controlled Trials (CENTRAL) (date of last search Sep 7, 2020). The latter includes the trial registries clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal. To identify potential additional eligible studies, we also screened the cited references and the citations (in Scopus) of three key publications in the field (PMIDs: 26898852, 30975736, 31662037). (Refs) We also identified any meta-analysis including such pertinent RCTs. The review was prospectively registered on PROSPERO (Registration Number on crd.york.ac.uk/PROSPERO CRD42020205295). Searches were done by information specialists from the University Library Basel.

3.3 Clinical evidence to date

We screened 7.902 records, out of which 10 eligible trials41-50 were found and two meta-analyses of seven RCTs7, 14. No RCT ever assessed whether EVT plus BMT in patients with an acute ischemic stroke due to a MeVO is superior to BMT alone for the reduction of the degree of disability and dependence in daily activities (measured with the mRS [modified rankin scale]) 90 days after the stroke. All trials examining the benefits of EVT primarily included patients with large vessel occlusions. Only 7.6% of the enrolled patients had a MeVO, prohibiting any evidence-based statement regarding the efficacy of EVT in this patient group.

Clinical evidence regarding large-vessel occlusions

In 2015, results from five large RCTs showed clear patient-relevant benefits with regard to disability or dependency in everyday activities (Odds Ratio (OR) 2.71, 95% Confidence Interval (CI) 2.07 – 3.55) of EVT in patients receiving or ineligible for intravenous thrombolysis (IVT) for an acute ischemic stroke due to a proximal large vessel occlusion (i.e. the intracranial carotid artery (ICA) or the M1 or dominant M2 segment of the middle cerebral artery) of the anterior circulation.(Refs) The average effect was substantial with a number needed to treat (NNT) to reduce disability by at least one level on the modified Rankin Scale (mRS) of 2.6.(Ref) However, the inclusion criteria of these trials resulted in large uncertainty regarding the applicability of the results to other groups of AIS patients, who are not treated routinely with EVT.

The main reason why physicians are reluctant to perform EVT in such patients are vessel occlusions that are "too" distal, even if baseline imaging suggests a high chance of EVT being beneficial.(Ref) These patients represent up to 50% of all patients with an intracranial vessel occlusion (according to data from the Swiss Stroke Registry and other large international registries).(Refs) In 2018, a meta-analysis used the individual patient level data of these five and two subsequently published trials with 131 M2 MCA patients (67 treated with EVT and 64 controls). The odds for less disability on the mRS scale was 1.68-fold higher with EVT but the confidence intervals were compatible with potential negative effects (OR 1.68 95% CI 0.90 – 3.14).(Ref) A further analysis of this data suggested a higher percentage of functionally independent patients (mRS ≤ 2) in the EVT group.

Limitations of available evidence and resulting uncertainty

The European Stroke Organization (ESO), the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the Stroke Alliance for Europe (SAFE) concluded that the data is insufficient to give a specific evidence-based recommendation for or against EVT in case of M2 occlusions.(Ref) The American Heart Association / American Stroke Association (AHA/ASA) also did not revisit their recommendation regarding the treatment of M2 occlusions.(Ref) … For other distal vessels, such as the M3 or M4 segment of the ACM and the ACA or PCA no randomized-controlled data is available.

This uncertainty regarding the treatment of such occlusions, results in markedly reduced treatment numbers and a high degree of variability in treatment decisions among clinicians. A large survey including more than 600 physicians using standardized case vignettes showed that in Europe roughly 40% would not pursue EVT in patients with M2 occlusions.(Refs) Even in relatively young patients (56-years old) in the early time-window (3 hours from symptom onset) with incapacitating deficits at presentation (global aphasia) and clear signs of salvageable penumbra only 56.4% of the clinicians decided in favour of EVT even under assumed perfect conditions.(Ref) For more distal occlusions such as M3 (18% treat first-line with EVT), A2 (40% treat first-line with EVT) or P2 (40% treat first-line with EVT) these rates are even lower.(Ref)

Interpretation of existing evidence

In summary, there is clinical equipoise regarding whether EVT in addition to BMT has a positive treatment effect in AIS patients with a MeVO and we therefore propose a pragmatic, randomized comparison of EVT plus BMT to BMT alone with the mRS after 90 days as the main outcome parameter."

REVEAL Working Definitions

Good-quality SR:

We consider a SR 'good-quality' if it is useful for the purpose of REVEAL. To qualify as 'good-quality', a SR should meet the following criteria (based on reasoning from AMSTAR2 and the "fast and frugal" decision tree): The search included at least 2 databases and a trial register, the search strategy was provided, risk of bias of included trials was systematically assessed, and a qualitative or quantitative synthesis of the trial results is included.

Recent or up-to-date SR:

Whether a SR can be considered 'recent' depends on the topic under investigation. In a fast-changing field, a SR with a search date of 2 years ago may be already out of date. In a field where developments are slower, a SR with a search date of, e.g., 5 years ago may still be usable; in particular, if a research question has been settled. As a rule of thumb, if you know already 1 or more RCTs not included in a SR due to an older search date, the SR should be considered 'outdated', but a SR with a search date of 1 year ago or less is typically considered 'recent'. In any case, we recommend consulting a content expert to judge whether the SR is outdated.

Sufficiently precise evidence:

Sufficiently precise evidence means that the width of 95% confidence intervals around effect estimates is narrow enough to classify the result as relevant benefit (i.e., the limits of the 95% confidence interval make no effect or harmful effects implausible), or to classify the result as no effect or harmful effect (i.e., the limits of the 95% confidence interval make a relevant benefit implausible).

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