Overview of Systematic Reviews

Systematic Review Training

Center for Knowledge Management

VANDERBILT UNIVERSITY MEDICAL CENTER

Objectives:

- ✓ Describe common reasons for conducting a systematic review
- ✓ Describe key steps in performing a systematic review
- ✓ Discuss time required to complete a systematic review

Why undertake a systematic review?

- Gather, appraise, and summarize best available evidence on a topic to create a comprehensive interpretation of research results
- Aid clinical decision-making by providing an independent, unbiased, objective assessment of the evidence
  - ❑ Practice guidelines
  - ❑ Assess effectiveness of health interventions
  - ❑ Determine effectiveness/accuracy of a diagnostic test
- Identify new research areas by determining when evidence on a topic is unavailable.

Additional reading:

Tina Poklepović Peričić and Sarah Tanveer. Why systematic reviews matter: a brief history, overview and practical guide for authors. July 23, 2019 https://www.elsevier.com/connect/authors-update/why-systematic-reviews-matter

Systematic Review Key Elements

- A systematic review comprises the ***entire process of collecting, reviewing*** (e.g., screening by two people, assigning strength of evidence (SOE), risk of bias assessment) and ***presenting all available evidence*** on a topic

- Conducted to bring together the best, strongest published literature to aid in decision-making by providing ***independent, unbiased, objective assessment of evidence***

- Topics are well defined by ***Key Questions*** devised in collaboration with experts in the field, and entire process is governed by a predefined ***Protocol***

- Requires ***team of topic experts*** & local workforce

- Workload spans ***1-2 years*** depending on topic

- Protocol is prospectively ***registered*** in an international database of SRs

Systematic :

- entire process is based on a method or plan *(protocol – just like a protocol undertaken in a lab, outlining step by step processes)*

- Characterized by order; methodical

Wordsmyth Adanced Dictionary. 2023. www.wordsmyth.net/?level=3&ent=systematic 7 March 2023

Borah R, Brown AW, Capers PL, Kaiser KA. Analysis of the time and workers needed to conduct systematic reviews of medical interventions using data from the PROSPERO registry. BMJ Open. 2017 Feb 27;7(2):e012545. doi: 10.1136/bmjopen-2016-012545. PMID: 28242767; PMCID: PMC5337708.

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

Flow diagram for systematic review steps

1 **Research Question & Assemble Team**
(Define population, intervention, comparator and outcomes)

2 **Preliminary search**
Validate idea does not appear in any journal or protocol, propose number of included studies

Summarize study idea and its importance to get members' attention for its global benefit on health and patients

Inclusion/exclusion criteria 3

4 **Define search terms and search strategies**

Search databases 5

PubMed: n= ( ) EMBASE: n= ( ) WoS: n = ( ) Cochrane: n = ( ) etc

Import into citation manager
Deduplicate database
Export to screening tool

Protocol writing & registration 6

Title and abstract screening by 2+ team members independently 7

Report number selected for full-text review

9 **Manual search**
- References from included studies
- Related articles / articles that cite included studies

Full-text downloading and screening by 2+ team members independently 8

Data extraction & quality assessment by 2+ team members independently
After pilot-testing extraction form and agreement 10

11 **Manuscript writing, revision, submission**

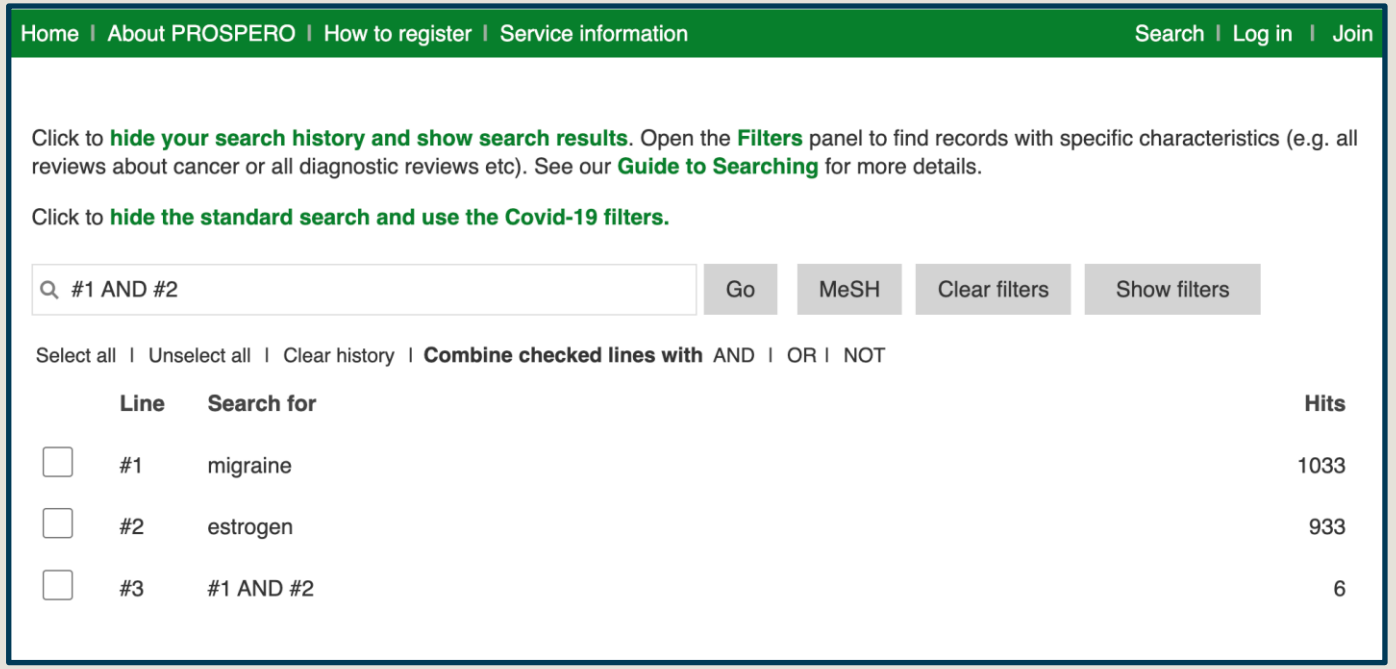
Adapted from Tawfik GM, Dila KAS, Mohamed MYF, Tam DNH, Kien ND, Ahmed AM, Huy NT. A step by step guide for conducting a systematic review and meta-analysis with simulation data. Trop Med Health. 2019 Aug 1;47:46. doi: 10.1186/s41182-019-0165-6. PMID: 31388330

1 Research Question: Verify systematic review isn't already being undertaken/done

PROSPERO

International prospective register of systematic reviews

- "International database of prospectively registered systematic reviews [PROTOCOLS] in health and social care"
- Permanent record
- Goal: provide "comprehensive listing of systematic reviews ***registered at inception***" and promote transparency of the processes
- Developed and managed by Centre for Reviews and Dissemination (CRD) at the Univ of York; funded by UK's National Institute of Health Research (NIHR)
- Free
- Cochrane protocols are automatically updated
- Protocols are editable
- After publication of findings, status should get updated in PROSPERO



https://www.crd.york.ac.uk/prospero/

Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L. PROSPERO at one year: an evaluation of its utility. Syst Rev. 2013 Jan 15;2:4. doi: 10.1186/2046-4053-2-4. PMID: 23320413; PMCID: PMC3563608.

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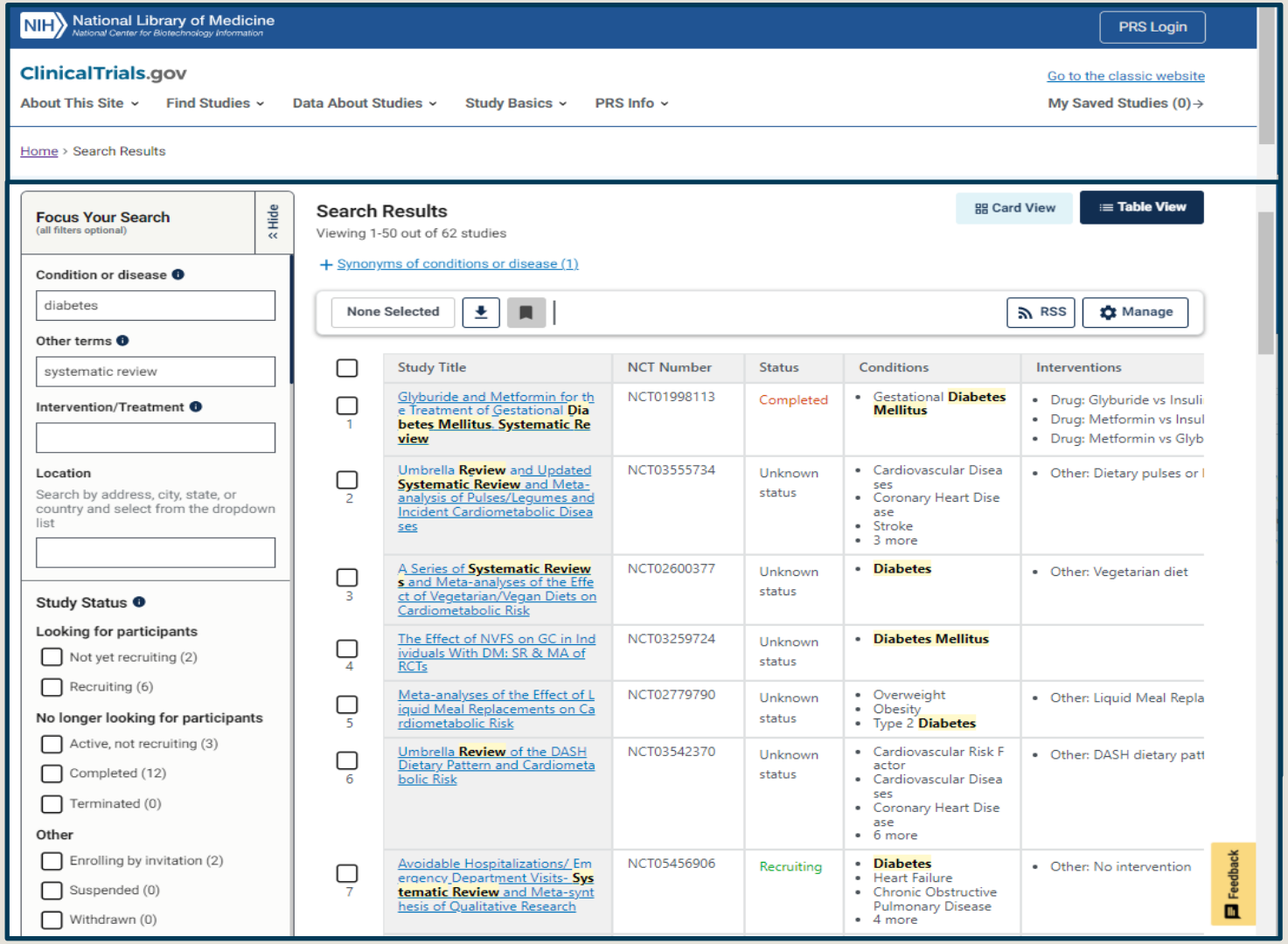

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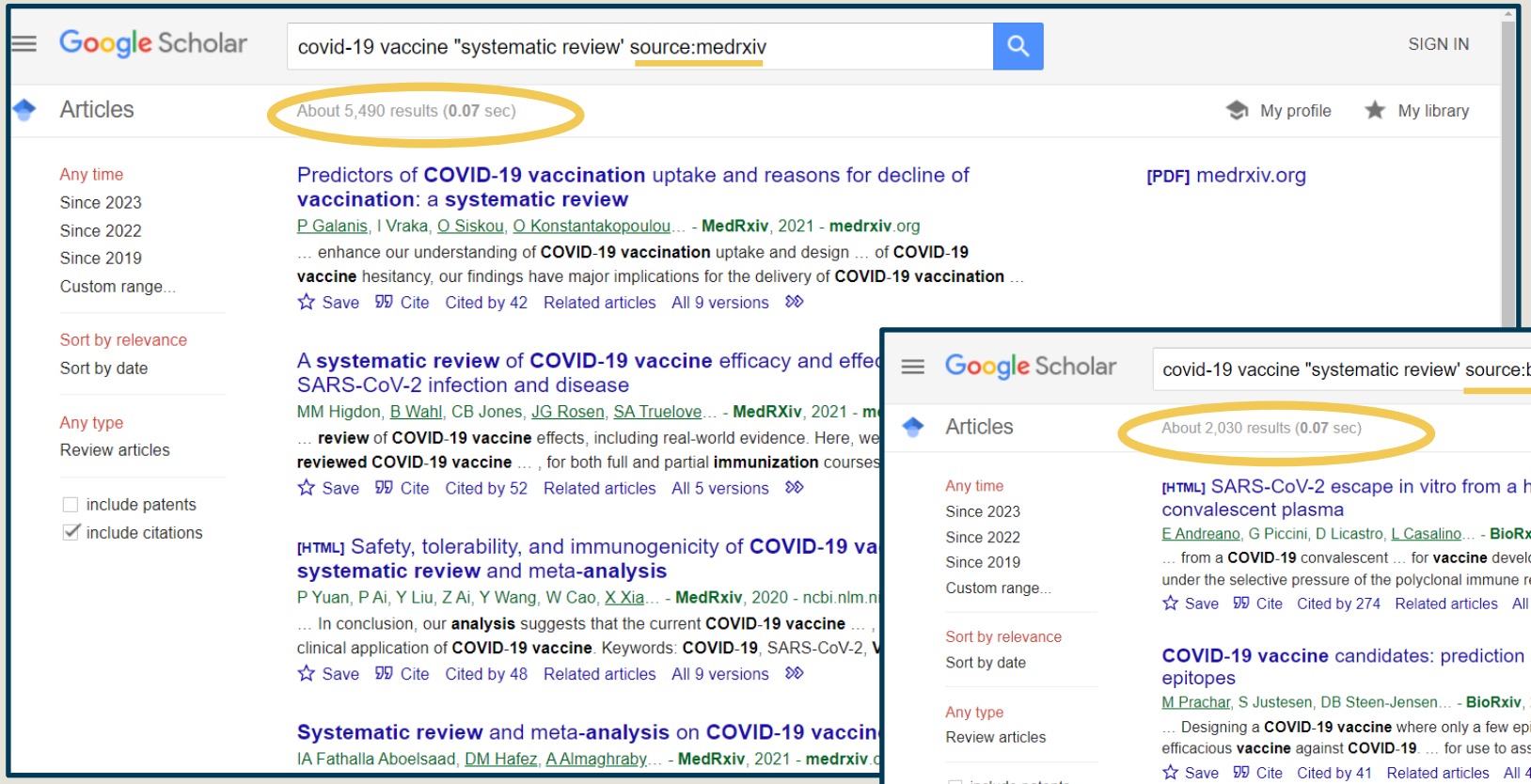
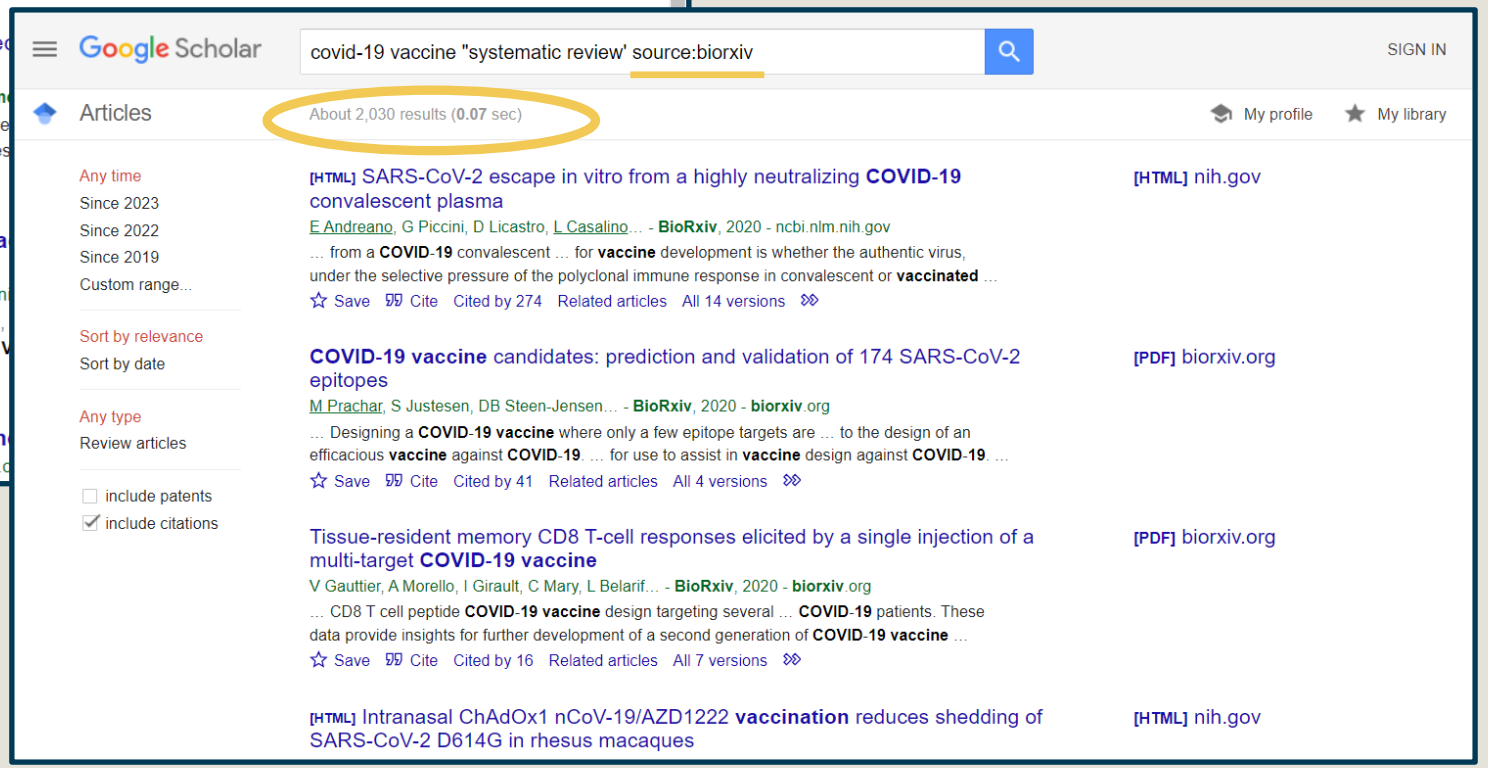


medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES
Cold Spring Harbor Laboratory BMJ Yale

https://www.medrxiv.org/content/about-medrxiv



Cold Spring Harbor Laboratory bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

https://www.biorxiv.org/submit-a-manuscript

1 Research Question: Verify systematic review isn't already being undertaken/done

("Migraine Disorders"[Mesh]) *with Systematic Review filter applied* = 572
"Migraine Disorders"[Mesh] AND systematic review[sb] = 572
[sb] = search tag for filters

PubMed filters use a search strategy to capture non-MEDLINE citations and citations that have not yet completed MEDLINE indexing in addition to citations assigned the systematic review publication type.

(((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]

Last reviewed: Feb 20, 2019

non-MEDLINE citations = citations from journals where articles are deposited in PMC *only* when they fall under NIH Public Access Policy

[ti] = title search; [ta] = publication title; [pt] = publication type

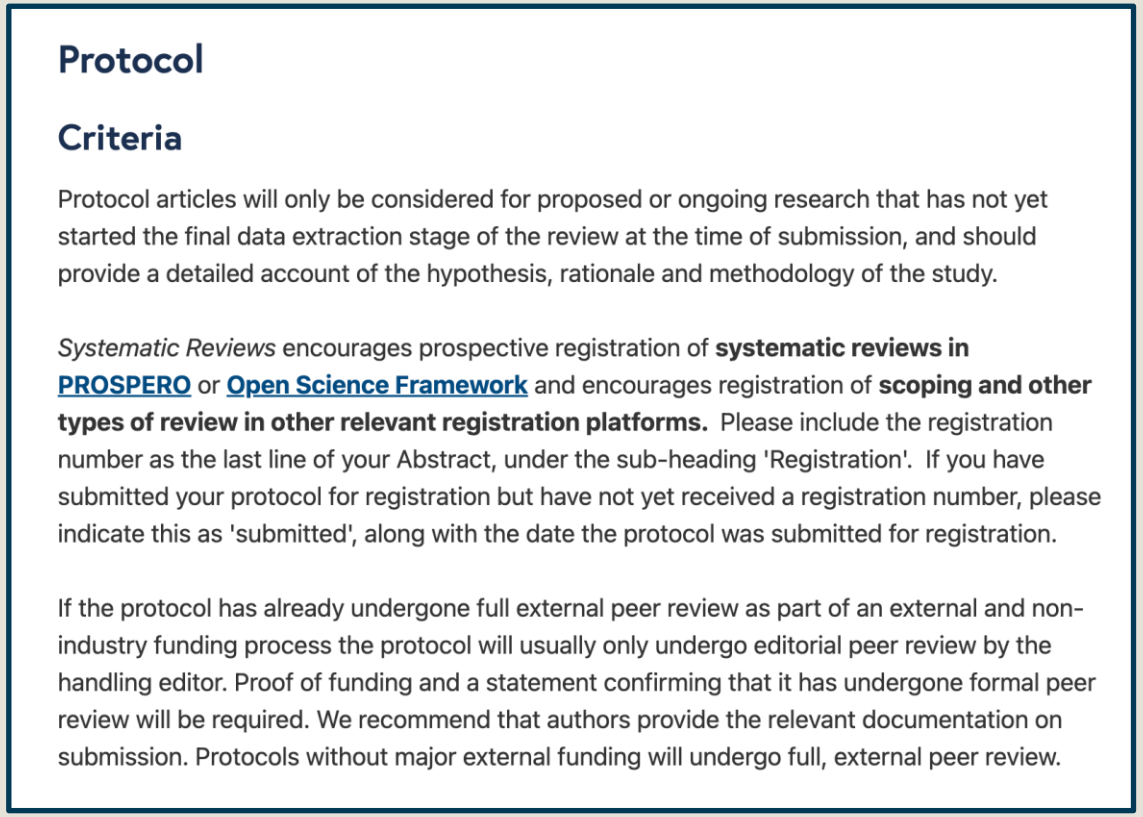
https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

1 Research Question: Verify systematic review isn't already being undertaken/done

- Protocols can be published independently of systematic reviews
- Top list of journals currently publishing protocols:
  - BMJ Open
  - Campbell Systematic Reviews
  - JBI Evidence Synthesis
  - Medicine (Baltimore)
  - PLoS One
  - Systematic Reviews

PubMed Search For Protocols:

("Systematic Reviews as Topic"[Mesh] OR "systematic review"[ti] OR "SR"[ti] OR "S.R."[ti]) AND ("protocol*"[ti]) AND (*Topic of interest*)



Protocol

Criteria

Protocol articles will only be considered for proposed or ongoing research that has not yet started the final data extraction stage of the review at the time of submission, and should provide a detailed account of the hypothesis, rationale and methodology of the study.

Systematic Reviews encourages prospective registration of **systematic reviews in PROSPERO** or **Open Science Framework** and encourages registration of **scoping and other types of review in other relevant registration platforms.** Please include the registration number as the last line of your Abstract, under the sub-heading 'Registration'. If you have submitted your protocol for registration but have not yet received a registration number, please indicate this as 'submitted', along with the date the protocol was submitted for registration.

If the protocol has already undergone full external peer review as part of an external and non-industry funding process the protocol will usually only undergo editorial peer review by the handling editor. Proof of funding and a statement confirming that it has undergone formal peer review will be required. We recommend that authors provide the relevant documentation on submission. Protocols without major external funding will undergo full, external peer review.

Criteria for publishing a protocol in Syst Rev.

Submission Guildelines [Internet]. BioMed Central; [cited 2023 Aug 22]. Available from: https://systematicreviewsjournal.biomedcentral.com/submission-guidelines/preparing-your-manuscript/protocol

1 Assembling the Team

- Recruit and establish a team with the ***appropriate expertise*** and ***experience*** to conduct the systematic review
- Be sure to include people with expertise in the clinical content, in systematic review methods, in searching, and in ***quantitative methods***
- Note: ***early in the process***, discuss who will be included as an author on the paper, and what his/her contributions will be.
- May need to have dedicated time for up to 2 years

Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Eden J, Levit L, Berg A, et al., editors. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US); 2011. https://www.ncbi.nlm.nih.gov/books/NBK209518/

1 Roles

Content experts -- local institution, beyond, noted in field; stakeholders who will benefit

Project manager -- keeps times, tracks progress, assigns work, is the "glue" for al the team members

Screeners -- commit to screen possibly thousands of titles/abstracts and then full-text. To avoid bias, each title/abstract and each article must be evaluated against key questions and inclusion/exclusion criteria *independently*

Adjudicators -- breaks ties/creates consensus

Database/searching expert -- with knowledge of broad scope of resources and unique searching syntax of each resource. Facility with citation mgmt.

Data extractors -- high attention to detail; expertise in understanding study outcomes

Statistician

Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Eden J, Levit L, Berg A, et al., editors. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US); 2011. *https://www.ncbi.nlm.nih.gov/books/NBK209518/*

1 Research Question: Formulate the Research Question

- Use a standard format for each question and clearly state the rationale for each question

- Use of the ***PICO formula*** can help clarify questions
  - ❑ population, intervention, comparator, outcomes

- ***Refine*** using ***stakeholder input*** as appropriate (includes content experts not involved in the systematic review)

- Could be ***iterative*** process based on findings from preliminary search of the literature

Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Eden J, Levit L, Berg A, et al., editors. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US); 2011. *https://www.ncbi.nlm.nih.gov/books/NBK209518/*

2 Preliminary Search

- Conduct ***exploratory searches*** (PubMed, EMBASE, etc) to investigate size of literature and if systematic review already exists
- If possible, identify ***seminal or landmark articles*** for building knowledgebase and familiarizing self with terminology
- Identify ***key articles*** known to be appropriate provides means of ***checking validity of search strategies***
- Will likely be ***iterative process***

Tawfik GM, Dila KAS, Mohamed MYF, Tam DNH, Kien ND, Ahmed AM, Huy NT. A step by step guide for conducting a systematic review and meta-analysis with simulation data. Trop Med Health. 2019 Aug 1;47:46. doi: 10.1186/s41182-019-0165-6. PMID: 31388330

3 Establishing Inclusion & Exclusion Criteria

- Should reflect the goals and **Key Questions**
  - **Types of participants**: Pediatric population? Should that include neonates? What about fetal and maternal health? Are adolescents included? What's the age restriction? 21? Americans? White women in the US and Europe? Black women in the U.S. with a confirmed COVID diagnosis?
  - **Types of studies**: only particular study designs? Exclude case reports, case series?
  - **Interventions:** pts 50-65yrs having undergone lobectomy within the past 2 years for early stage lung cancer
  - **Outcomes sought:** effect of pulmonary rehab on pts with COPD following lobectomy
- Defining your inclusion criteria ***broadly*** results in a larger view of what is known/published
- Defining it ***too* broadly** results in too much literature to review and likely a lot of heterogeneous literature
- Defining your ***inclusion criteria narrowly*** results in a smaller pool of literature to review
- However, defining your inclusion criteria **too narrowly** can negatively affect the validity/applicability of the review

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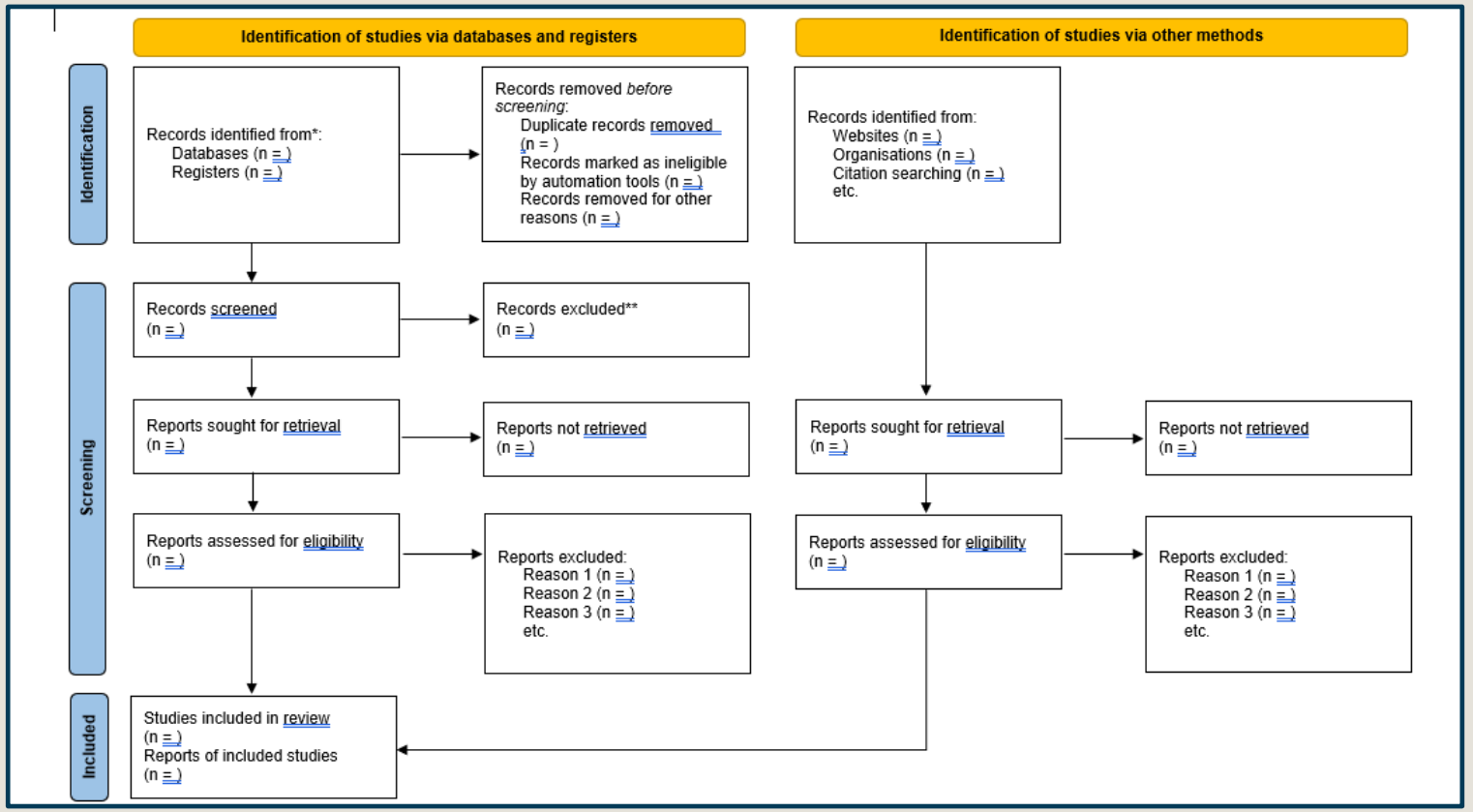
3 Establishing Inclusion & Exclusion Criteria

PRISMA 2020 Flow Diagram (also called Disposition of records)



http://www.prisma-statement.org/PRISMAStatement/FlowDiagram

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

4 Defining search terms and strategies

5 Search databases

Defining search terms and search strategies

See lecture video:
Systematic Review Search Strategies

Search databases

See lecture videos:
Systematic Review Search Strategies
&
Article Selection

6 Protocol Writing & Registration

- PRISMA – P can guide you
- Explicitly documents rationale & purpose, and plan up front to allow others to compare protocol with final product (for replication, transparency and mitigate risks of selective reporting)
- Registered protocols can reduce redundant efforts by other teams
- Prospero – international, prospective register for SR protocols

Centre for Reviews and Dissemination at the University of York (UK)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

6 Protocol Writing & Registration

- PROSPERO is an “International database of prospectively registered systematic reviews [PROTOCOLS] in health and social care”
  - Free
  - Protocols are editable
  - After publication of findings, status should get updated in PROSPERO
- Other options for registration:
  - Campbell Collaboration
    - Social science research – focused on social interventions
  - CAMRADES (Collaborative Approach to Meta-analysis and Review of Animal Data from Experimental Studies)
    - Focus on translational medicine

https://www.crd.york.ac.uk/prospero/
https://www.campbellcollaboration.org/
https://www.ed.ac.uk/clinical-brain-sciences/research/camarades

7 Title and abstract screening

- Series of questions to be considered for all eligible articles by 2 independent screeners
- Inclusion and Exclusion criteria are translated into questions, e.g.:
  - Is this original research? Is it published in English?
  - Does it involve human subjects? Does the study include patients under 18 years old?
  - Is the patient population of the study of eligible size?
  - Does the study address the specifically targeted interventions or conditions?
- Screeners don't agree: automatically moves on to fulltext screening
- No abstract: automatically moves on to fulltext screening
- Good to include comments field or pick list to indicate "save for background" or "check references"
- All screener responses must be documented

Tawfik GM, Dila KAS, Mohamed MYF, Tam DNH, Kien ND, Ahmed AM, Huy NT. A step by step guide for conducting a systematic review and meta-analysis with simulation data. Trop Med Health. 2019 Aug 1;47:46. doi: 10.1186/s41182-019-0165-6. PMID: 31388330

Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

8 Full-text screening

- Contains more detailed questions (from key questions) than title/abstract review
  - Inclusion/exclusion criteria
  - Questions may help categorize ("bucket") studies
- Screeners don't agree → goes for adjudication
- Good to include comments field or pick list to indicate "save for background" or "check references"
- All screener responses must be documented

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9 Manual search (hand searching)

- References from included studies
- Related articles / articles that cite included studies
- Articles found by hand searching must go through entire screening process
- Important to keep notes on how each one was discovered

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10

Data extraction

- Papers that are included after full-text review
- Pull key data from each article and into a table
  - Discuss data to include before starting
- Purpose/goals:
  - Surrogate, or “at-a-glance” reference, for full paper in the final report
  - Helps to categorize/compare studies
  - Aid in drafting content of report
  - Data can be pulled into summary tables in the text

Quality Assessment

- Strength of the evidence: assessment of methodologic quality ***across the pool of studies for a given intervention***
- Use tools, such as the Cochrane risk of bias assessment
- Dual review process

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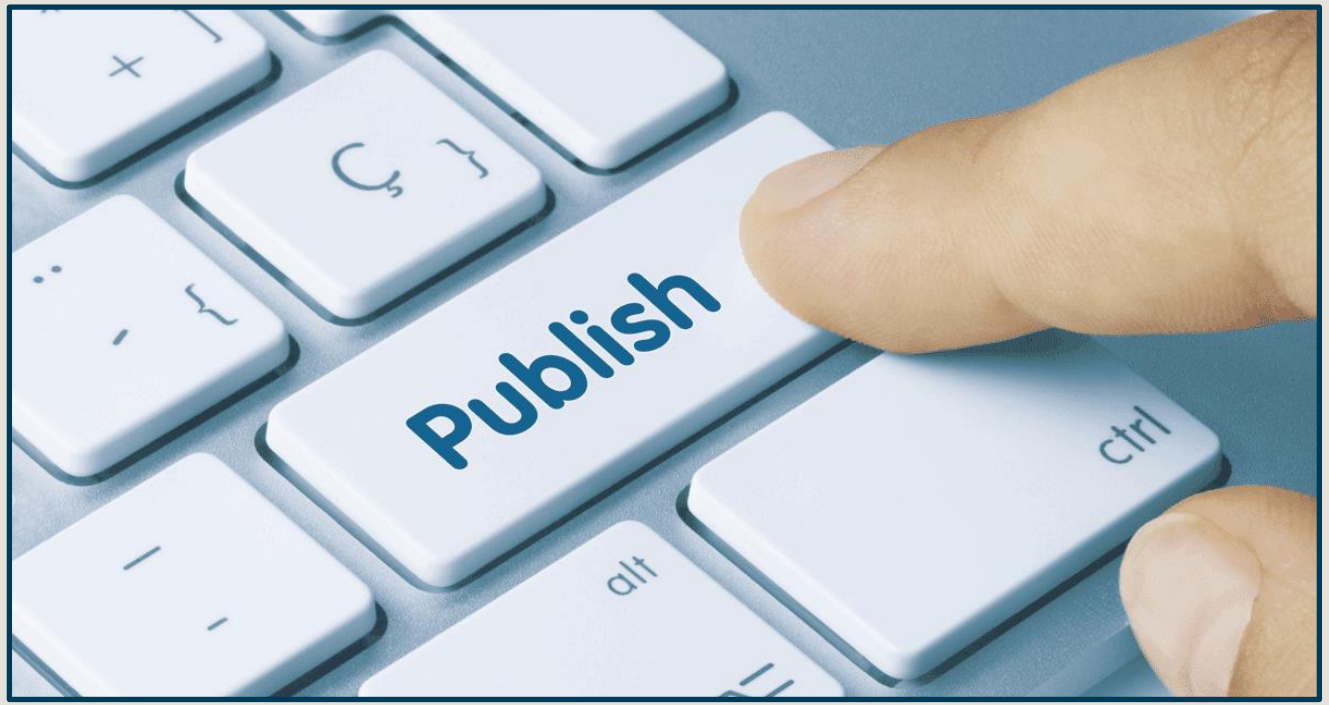
11 Manuscript writing, revision, submission

- Considerations:
  - Relevance of journal focus
  - What journals are clinicians who need this information reading?
  - Submission criteria
  - Impact factor and reputation



[note: publishing process is different for Cochrane, AHRQ reviews]

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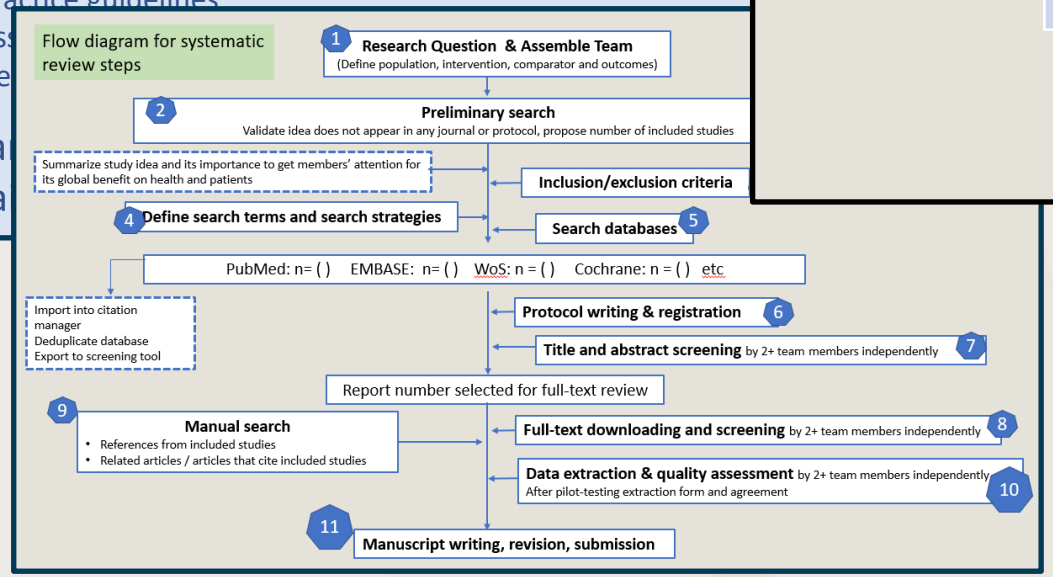
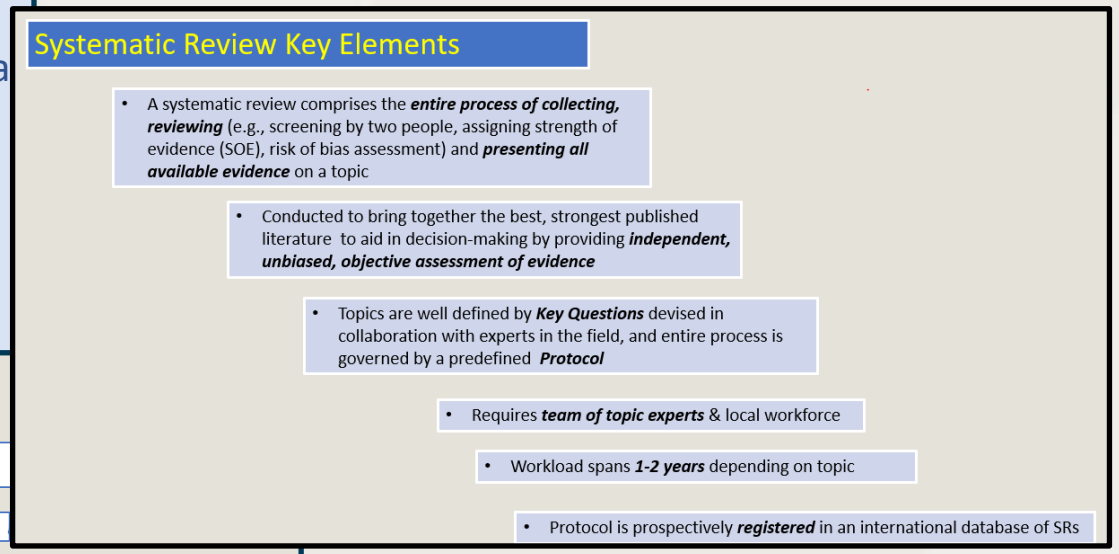
Module recap

Why undertake a systematic review?

- Gather, appraise, and summarize best available evidence on a topic to create a comprehensive interpretation of research results
- Aid clinical decision-making by providing an independent, unbiased, objective assessment of the evidence
  - ❑ Practice guidelines
  - ❑ Ass
  - ❑ De
- Identify new resea
  on a topic is unava





Presented by

Center for Knowledge Management

VANDERBILT UNIVERSITY

MEDICAL CENTER