NIHR | Newcastle In Vitro Diagnostics Co-operative

Academic Health Science Network North East and North Cumbria

Introduction to Systematic Review Methodology

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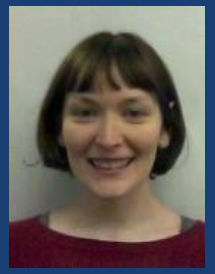

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Objectives of this session….

- Explain what a systematic review is and the reasons for undertaking this type of research
- Describe the different stages of the systematic review process
- Identify components of a systematic review research question

Literature review

- What is the purpose of a literature review?

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  - *a) summarise existing evidence*
  - *b) make the results of multiple studies more accessible for policy makers*
  - *c) provide a more definite answer then looking at one study on it's own*
  - *d) all of the above*

- A review can either be systematic or rapid

Literature review

- "*a review of the evidence based on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise [all] relevant primary research, and to extract and analyse data from the studies that are included in the review*." (Cochrane Public Health)
- A review can either be rapid or systematic:

	Rapid	Systematic
Timeframe	Can take up to 6 months	Often take 12-24 months
Resources	Sources are limited due to time constraints of searching	Comprehensive
Searches	May apply limits e.g. language	Comprehensive
Synthesis	Narrative summary of findings	Narrative & maybe meta-analysis
Rigor	More susceptible to bias	Maintain methodological rigor & ensure validity

Why conduct a systematic review?

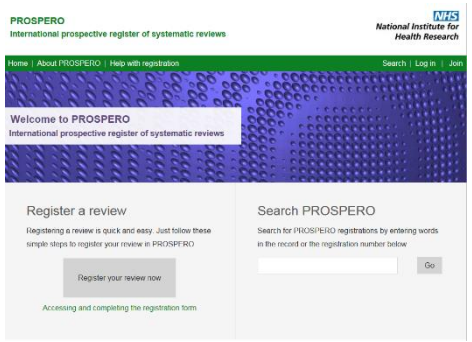
- More precise estimate of an association or effect
- To inform clinical decision making
- To inform policies and guidance
- Identify research gaps and areas for further research

Types of systematic review questions

Question	Explanation	Example	Ideal study type
Aetiology and risk factors	Are there known factors that increase the risk of disease?	Is smoking associated with increased risk of lung cancer?	Cohort
Interventions	What are the effects of an intervention?	Is vitamin C effective for preventing the common cold?	RCTs
Frequency or rate of a condition or disease	How common is a condition or disease in a specified group?	Quantify the global variation in childhood myopia prevalence	Cross-sectional studies
Prediction and prognosis	Can the risk for an individual be predicted?	Predicting of myopia progression in school children	Cohort
Diagnostic accuracy	How accurate is a particular diagnostic screening test?	Diagnostic accuracy of screening tests for COPD confirmed by spirometry in primary care	Randomised or consecutive sample
Phenomena	What phenomena have been observed in a particular clinical problem?	Barriers to the uptake of eye care services	Qualitative (e.g. focus groups; semi-structured interviews)

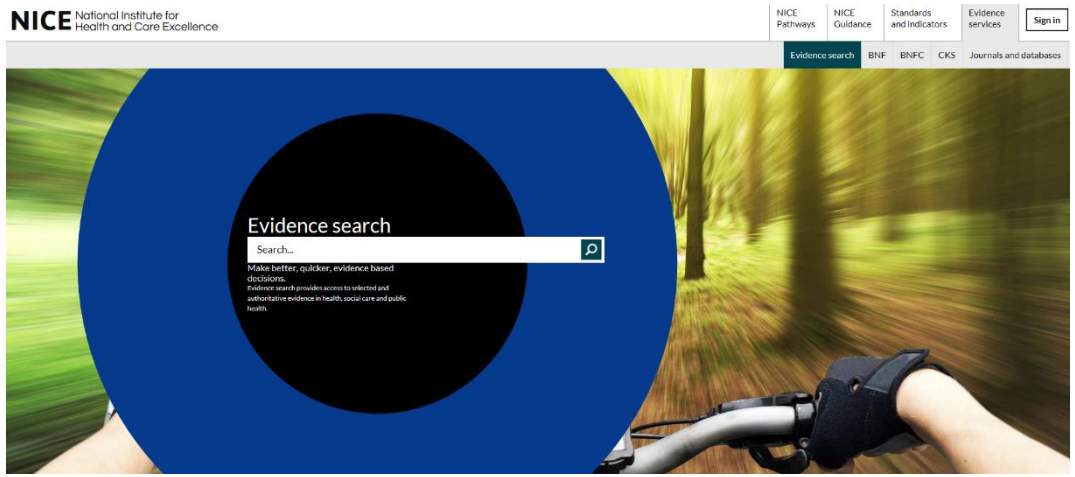
Questions

Check whether a new review is justified



Cochrane Library

Trusted evidence.
Informed decisions.
Better health.



Steps in conducting a systematic review

1. Plan the review and formulate your question
2. Develop a protocol and search strategy
3. Conduct searches for relevant studies
    a) Screen title and abstracts for possible inclusion
    b) Screen full papers and citations for inclusion in the review
4. Develop data extraction form, pilot, extract data
5. Assess the quality of the included studies
6. Undertake data analysis and synthesis
7. Interpret results and prepare report/paper

Formulate a research question

- P = population
- I = index test (test under examination)
- C = comparison or reference test (gold standard)
- O = outcome
- S = study design

- Your research question will inform your search strategy

- *Robert L. Schmidt and Rachel E. Factor (2013) Understanding Sources of Bias in Diagnostic Accuracy Studies. Archives of Pathology & Laboratory Medicine: April 2013, Vol. 137, No. 4, pp. 558-565.*

Activity

Identify elements of the PICOS in the following research question:

The diagnostic accuracy of high resolution ultrasound, fine needle aspiration or core biopsy to detect recurrence and locoregional metastases during surveillance in patients with melanoma.

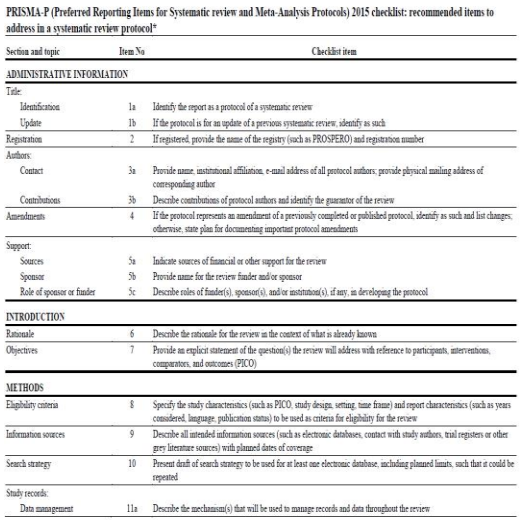
Answers

Identify elements of the PICOS in the following research question:

The diagnostic accuracy of high resolution ultrasound, fine needle aspiration or core biopsy (index test) to detect recurrence and locoregional metastases (outcomes) during surveillance in patients with melanoma (patients).

Develop a protocol, publish this on PROSPERO

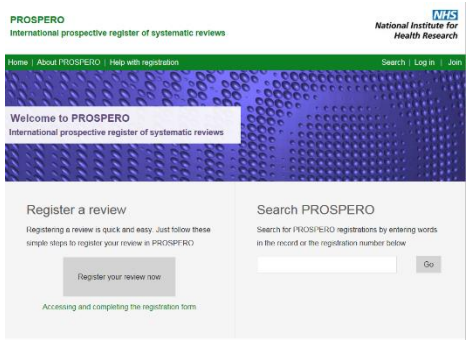
- Background
- Review question
- Inclusion and exclusion criteria
- Identify research evidence
- Study selection
- Data extraction
- Risk of bias assessment
- Data synthesis
- Time plan
- Dissemination plan



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

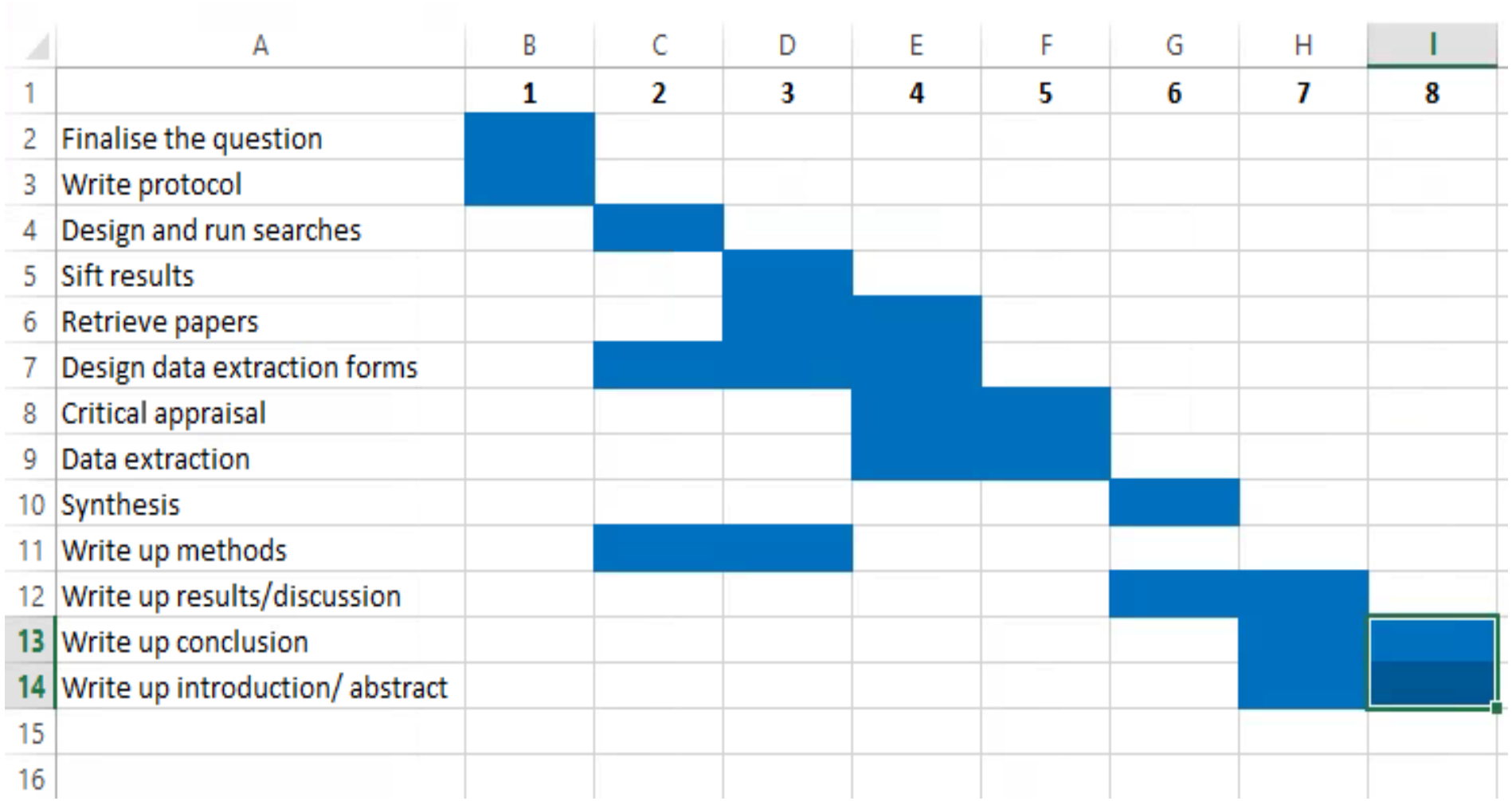
Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the 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

http://www.prisma-statement.org/PRISMAStatement/Checklist.aspx



http://www.crd.york.ac.uk/PROSPERO/

Gantt chart– example in Excel



	A	B	C	D	E	F	G	H	I
1		1	2	3	4	5	6	7	8
2	Finalise the question								
3	Write protocol								
4	Design and run searches								
5	Sift results								
6	Retrieve papers								
7	Design data extraction forms								
8	Critical appraisal								
9	Data extraction								
10	Synthesis								
11	Write up methods								
12	Write up results/discussion								
13	Write up conclusion								
14	Write up introduction/ abstract								
15									
16									

Searching for literature

The diagnostic accuracy of high resolution ultrasound, fine needle aspiration or core biopsy to detect recurrence and locoregional metastases during surveillance in patients with melanoma.

What search terms will you use?

Population	Index test	Outcomes
Melanoma Skin neoplasms tumour	Ultrasound Ultrasonography Fine needle biopsy Fine needle aspiration Core needle biopsy	Sensitivity Specificity Probability Recurrence Likelihood ratios Diagnostic odds ratio False positive rate Summary receiver operating curves

Also consider:
Synonyms - e.g. ultrasound: sonography, ultrasonography
Plurals - e.g. biopsy or biopsies
Spelling variants (UK vs US) e.g. randomise/randomize

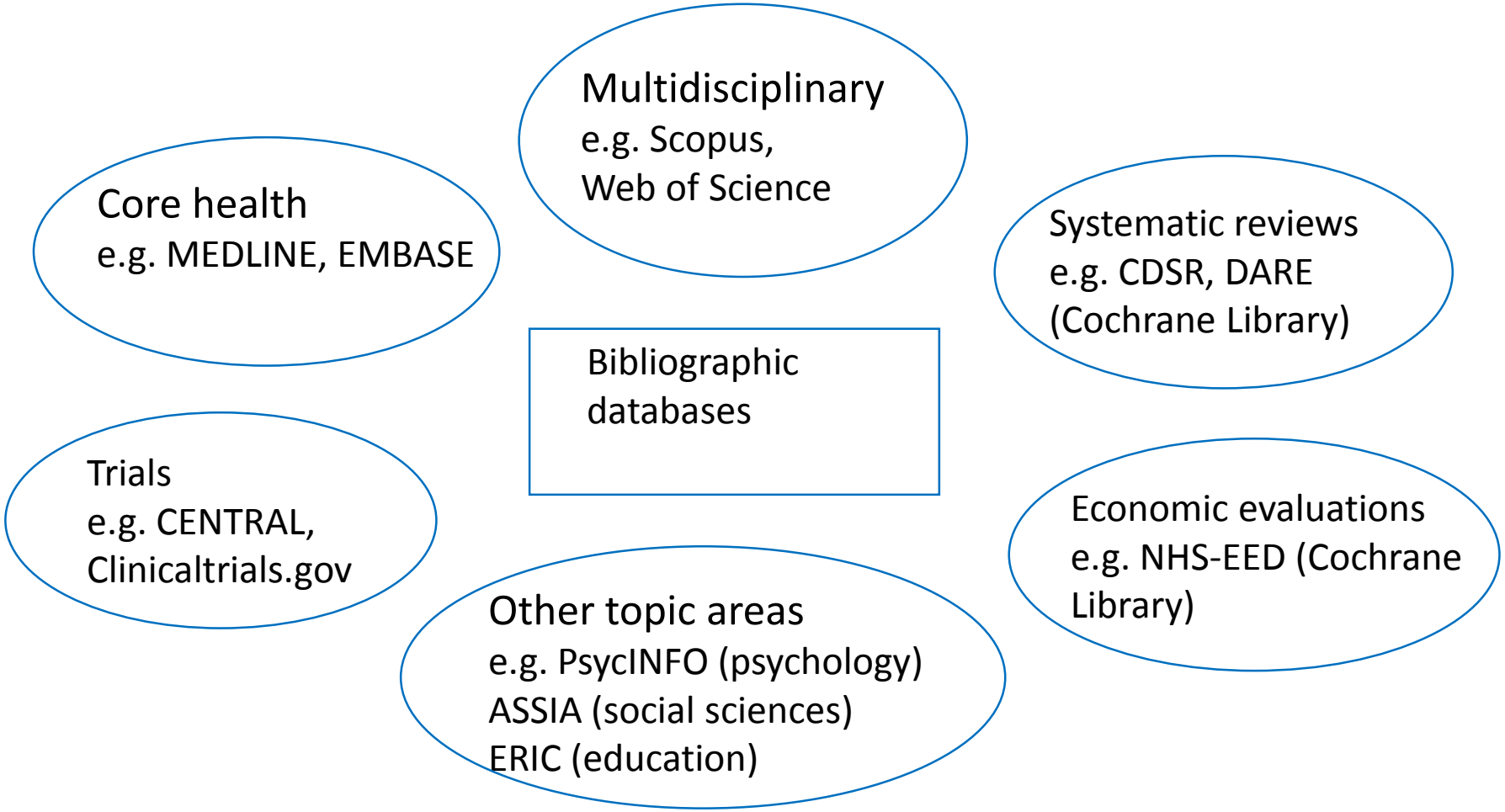
Advanced skills

- **Truncation** – allows stemming (e.g. diagnos* = diagnosis, diagnostic)
- **Wildcard** – can be used for variant spellings (e.g. randomi$ed = randomised or randomized)
- **Phrase searching** – place inverted commas/quotations around phrase to retrieve *exact* phrase (e.g. “skin neoplasms”)
- **Proximity** – tumo* adj5 (mole or melanoma)

Not all databases support this form of searching and the symbols may vary!

Some tools available to translate search strategies across databases, e.g.
https://medlinetranspose.github.io/index.html

Where will you look?
Bibliographic databases



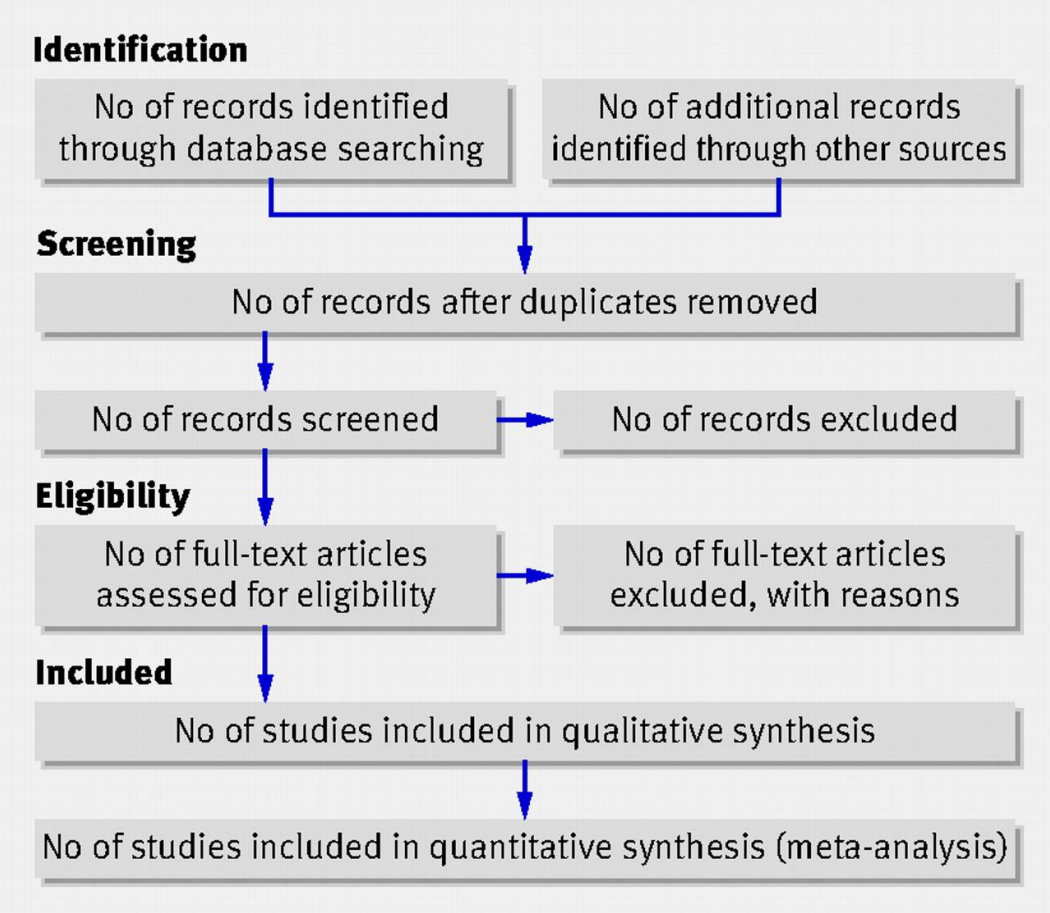
Study selection

- Reference manager software package (e.g. Endnote; Rayyan).

Two stages:

1. Screening of titles and abstracts against eligibility criteria
2. Screening of full papers identified as possibly relevant

Flow of include and excluded studies



Data extraction

Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
METHODS		
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	**6**	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test methods	**10a**	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard

- Data extracted from each included study will be based upon the Standards for Reporting Diagnostic Accuracy (STARD 2015) checklist
- Data extracted from each study will be verified independently by a different reviewer
- Any disagreements are referred to a third researcher for resolution
- Studies reported by the same centres with overlapping populations are selected for inclusion we will use the most recent publication reporting the full data set required for diagnostic test performance

Risk of bias assessment

What is bias?

Systematic error or deviation from the truth = wrong association between intervention and outcome.

Types of bias:

- Selection bias – allocation sequence concealment
- Performance bias – blinding not always possible
- Detection bias – blinding assessors
- Reporting bias – only reporting differences
- Attrition bias – unequal loss of participants

Tools for assessing risk of bias

- Cochrane risk of bias tool (RCTs): low, moderate or high risk of bias
- ROBINS-I (non-randomized, quantitative studies: quasi-experimental studies, cohort studies, case-control studies, cross-sectional studies)
- Critical Appraisal Skills Programme (tools for various study designs, including qualitative)
- QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool

Questions

Data synthesis (1) narrative synthesis

Results from different studies need to be synthesised

All systematic reviews narrative synthesis.

- Tabulate study characteristics
- Arrange studies in groups
- Report the same information in the same order for each study
- Best available evidence approach
- Examination of moderator variables

Data synthesis (2) meta-analysis

- A statistical analysis which combines the results of several independent studies examining the same question
- Explains observed heterogeneity in the results of studies included in the review
- Usually done using specialised statistical software:
  - RevMan
  - Stata
  - SPSS
  - SAS
  - R
- For systematic reviews of medical tests, a meta-analysis often focuses on synthesis of test performance data (Borenstein et al., 2009)

Checklist of items to include when reporting a systematic review or meta-analysis.

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine 6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097
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- PROSPERO http://www.crd.york.ac.uk/prospero/about.php?about=citerecord
- Rayyan https://rayyan.qcri.org/
-
- Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. http://www.prisma-statement.org
-
- The Cochrane Library http://www.thecochranelibrary.com/

Thank you

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