Systematic Review

Seyed Aria Nejadghaderi, MD-MPH

HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

Emails: a.nejadghaderi@kmu.ac.ir; ariang20@gmail.com

Outline

- Introduction to systematic review
- Formulating research questions
- Developing protocols
- Search strategy
- Study selection
- Additional search
- Data extraction and quality assessment
- Data synthesis
- Drafting the manuscript

What is a Review?

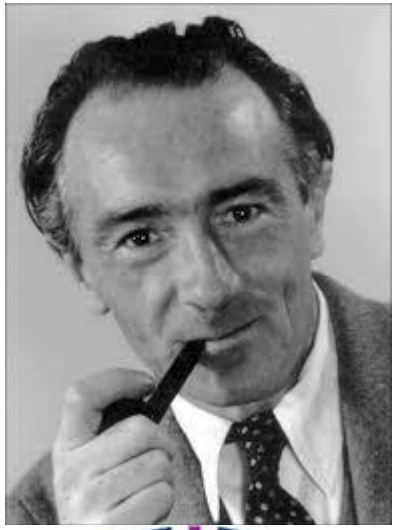
- Definition:
  - A review does not present new data but assesses what has already been published or presented on a particular topic.
- Purpose:
  - Reviews provide a synthesis of existing knowledge, summarizing and analyzing the literature to identify key insights, trends, or gaps.

History of Systematic Reviews

- Part of the broader "evidence movement," which aims to organize knowledge into reliable and accessible formats.
- Systematic methods for appraising and synthesizing evidence emerged in the 1970s.
- **Introduction of Meta-Analysis (1975)**
  - Coined by Gene Glass to systematically synthesize research findings.

History of Systematic Reviews Cont.

- Evidence-Based Medicine (EBM) Concept:
  - Introduced by Archie Cochrane in Effectiveness and Efficiency (1972).
  - Defined by David Sackett (1996) as the “conscientious, explicit, judicious use of current best evidence” in clinical decision-making.
- The Cochrane Collaboration (1992):
  - Established by a network of health researchers in Oxford.
  - Focused on systematic reviews of healthcare interventions.
  - Became an international organization committed to quality-assured, accessible, and cumulative healthcare evidence.



Cochrane

History of Systematic Reviews Cont.

- Expansion Beyond Medicine: The Campbell Collaboration (2000):
  - Adapted Cochrane methods to public policy areas like education, social welfare, and crime prevention.
  - Extended systematic evidence synthesis to broader fields.
- The EPPI Centre (1992):
  - Created at the Institute of Education, University of London, to review interventions in education and social welfare.
  - Expanded to health promotion, social care, and employment.
  - Supported systematic reviews in education.
  - Developed methods for diverse research questions, becoming a hub for systematic synthesis in multiple fields.

Types of Review Articles

- Systematic Review: Structured, Focuses on a narrow question with predefined methods.
- Narrative Review: Flexible, thematic, and qualitative. Provides a broad overview of a topic.
- Meta-Analysis: Statistically combines results from multiple studies.
- Scoping Review: Maps existing literature on a broad topic.
- State-of-the-Art Review: Summarizes current knowledge and future directions.
- Umbrella Review: Reviews other reviews.

Types Of Review Articles	
Critical Review	Meta-Analysis
Overview	Mixed Studies Review
Narrative Review	Systematic Qualitative Review
Rapid Review	Systematic Quantitative Review
Scoping Review	State-of-the-Art Review
Mapping Review	Systematic Search/Review
Systematized Review	Cochrane Review
Umbrella Review	Campbell Collaboration Review

Chaney MA. So you want to write a narrative review article?. Journal of Cardiothoracic and Vascular Anesthesia. 2021 Oct 1;35(10):3045-9.

Main Review Types

Table 1 Main review types characterized by methods used

		Methods used (SALSA)			
Label	Description	Search	Appraisal	Synthesis	Analysis
Critical review	Aims to demonstrate writer has extensively researched literature and critically evaluated its quality. Goes beyond mere description to include degree of analysis and conceptual innovation. Typically results in hypothesis or model	Seeks to identify most significant items in the field	No formal quality assessment. Attempts to evaluate according to contribution	Typically narrative, perhaps conceptual or chronological	Significant component: seeks to identify conceptual contribution to embody existing or derive new theory
Literature review	Generic term: published materials that provide examination of recent or current literature. Can cover wide range of subjects at various levels of completeness and comprehensiveness. May include research findings	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative	Analysis may be chronological, conceptual, thematic, etc.
Mapping review/ systematic map	Map out and categorize existing literature from which to commission further reviews and/or primary research by identifying gaps in research literature	Completeness of searching determined by time/scope constraints	No formal quality assessment	May be graphical and tabular	Characterizes quantity and quality of literature, perhaps by study design and other key features. May identify need for primary or secondary research
Meta-analysis	Technique that statistically combines the results of quantitative studies to provide a more precise effect of the results	Aims for exhaustive, comprehensive searching. May use funnel plot to assess completeness	Quality assessment may determine inclusion/ exclusion and/or sensitivity analyses	Graphical and tabular with narrative commentary	Numerical analysis of measures of effect assuming absence of heterogeneity
Mixed studies review/mixed methods review	Refers to any combination of methods where one significant component is a literature review (usually systematic). Within a review context it refers to a combination of review approaches for example combining quantitative with qualitative research or outcome with process studies	Requires either very sensitive search to retrieve all studies or separately conceived quantitative and qualitative strategies	Requires either a generic appraisal instrument or separate appraisal processes with corresponding checklists	Typically both components will be presented as narrative and in tables. May also employ graphical means of integrating quantitative and qualitative studies	Analysis may characterise both literatures and look for correlations between characteristics or use gap analysis to identify aspects absent in one literature but missing in the other
Overview	Generic term: summary of the [medical] literature that attempts to survey the literature and describe its characteristics	May or may not include comprehensive searching (depends whether systematic overview or not)	May or may not include quality assessment (depends whether systematic overview or not)	Synthesis depends on whether systematic or not. Typically narrative but may include tabular features	Analysis may be chronological, conceptual, thematic, etc.
Qualitative systematic review/qualitative evidence synthesis	Method for integrating or comparing the findings from qualitative studies. It looks for 'themes' or 'constructs' that lie in or across individual qualitative studies	May employ selective or purposive sampling	Quality assessment typically used to mediate messages not for inclusion/exclusion	Qualitative, narrative synthesis	Thematic analysis, may include conceptual models

Grant, M.J. and Booth, A. (2009), A typology of reviews: an analysis of 14 review types and associated methodologies. Health Information & Libraries Journal, 26: 91-108. https://doi.org/10.1111/j.1471-1842.2009.00848.x

Main Review Types Cont.

Table 1 *Continued*

		Methods used (SALSA)			
Label	Description	Search	Appraisal	Synthesis	Analysis
Rapid review	Assessment of what is already known about a policy or practice issue, by using systematic review methods to search and critically appraise existing research	Completeness of searching determined by time constraints	Time-limited formal quality assessment	Typically narrative and tabular	Quantities of literature and overall quality/direction of effect of literature
Scoping review	Preliminary assessment of potential size and scope of available research literature. Aims to identify nature and extent of research evidence (usually including ongoing research)	Completeness of searching determined by time/scope constraints. May include research in progress	No formal quality assessment	Typically tabular with some narrative commentary	Characterizes quantity and quality of literature, perhaps by study design and other key features. Attempts to specify a viable review
State-of-the-art review	Tend to address more current matters in contrast to other combined retrospective and current approaches. May offer new perspectives on issue or point out area for further research	Aims for comprehensive searching of current literature	No formal quality assessment	Typically narrative, may have tabular accompaniment	Current state of knowledge and priorities for future investigation and research
Systematic review	Seeks to systematically search for, appraise and synthesis research evidence, often adhering to guidelines on the conduct of a review	Aims for exhaustive, comprehensive searching	Quality assessment may determine inclusion/exclusion	Typically narrative with tabular accompaniment	What is known; recommendations for practice. What remains unknown; uncertainty around findings, recommendations for future research
Systematic search and review	Combines strengths of critical review with a comprehensive search process. Typically addresses broad questions to produce 'best evidence synthesis'	Aims for exhaustive, comprehensive searching	May or may not include quality assessment	Minimal narrative, tabular summary of studies	What is known; recommendations for practice. Limitations
Systematized review	Attempt to include elements of systematic review process while stopping short of systematic review. Typically conducted as postgraduate student assignment	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative with tabular accompaniment	What is known; uncertainty around findings; limitations of methodology
Umbrella review	Specifically refers to review compiling evidence from multiple reviews into one accessible and usable document. Focuses on broad condition or problem for which there are competing interventions and highlights reviews that address these interventions and their results	Identification of component reviews, but no search for primary studies	Quality assessment of studies within component reviews and/or of reviews themselves	Graphical and tabular with narrative commentary	What is known; recommendations for practice. What remains unknown; recommendations for future research

Grant, M.J. and Booth, A. (2009), A typology of reviews: an analysis of 14 review types and associated methodologies. Health Information & Libraries Journal, 26: 91-108. https://doi.org/10.1111/j.1471-1842.2009.00848.x

Narrative Review

Narrative review

Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review

Thibault Fiolet [1,*], Yousra Kherabi [2,3], Conor-James MacDonald [1], Jade Ghosn [2,3], Nathan Peiffer-Smadja [2,3,4]

[1] *Paris-Saclay University, UVSQ, INSERM, Gustave Roussy, 'Exposome and Heredity' team, CESP UMR1018, Villejuif, France*
[2] *Université de Paris, IAME, INSERM, Paris, France*
[3] *Infectious and Tropical Diseases Department, Bichat-Claude Bernard Hospital, AP-HP, Paris, France*
[4] *National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College, London, UK*

ARTICLE INFO

Article history:
Received 3 August 2021
Received in revised form
7 October 2021
Accepted 16 October 2021
Available online 27 October 2021

Editor: L. Kaiser

Keywords:
Coronavirus
COVID-19
Delta
Efficacy
Review
SARS-CoV-2
Seroneutralization
Vaccines
Variants

ABSTRACT

Background: Vaccines are critical cost-effective tools to control the coronavirus disease 2019 (COVID-19) pandemic. However, the emergence of variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may threaten the global impact of mass vaccination campaigns.
Aims: The objective of this study was to provide an up-to-date comparative analysis of the characteristics, adverse events, efficacy, effectiveness and impact of the variants of concern for 19 COVID-19 vaccines.
Sources: References for this review were identified through searches of PubMed, Google Scholar, BioRxiv, MedRxiv, regulatory drug agencies and pharmaceutical companies' websites up to 22nd September 2021.
Content: Overall, all COVID-19 vaccines had a high efficacy against the original strain and the variants of concern, and were well tolerated. BNT162b2, mRNA-1273 and Sputnik V after two doses had the highest efficacy (>90%) in preventing symptomatic cases in phase III trials. mRNA vaccines, AZD1222, and CoronaVac were effective in preventing symptomatic COVID-19 and severe infections against Alpha, Beta, Gamma or Delta variants. Regarding observational real-life data, full immunization with mRNA vaccines and AZD1222 seems to effectively prevent SARS-CoV-2 infection against the original strain and Alpha and Beta variants but with reduced effectiveness against the Delta strain. A decline in infection protection was observed at 6 months for BNT162b2 and AZD1222. Serious adverse event rates were rare for mRNA vaccines—anaphylaxis 2.5–4.7 cases per million doses, myocarditis 3.5 cases per million doses—and were similarly rare for all other vaccines. Prices for the different vaccines varied from $2.15 to $29.75 per dose.
Implications: All vaccines appear to be safe and effective tools to prevent severe COVID-19, hospitalization, and death against all variants of concern, but the quality of evidence greatly varies depending on the vaccines considered. Questions remain regarding a booster dose and waning immunity, the duration of immunity, and heterologous vaccination. The benefits of COVID-19 vaccination outweigh the risks, despite rare serious adverse effects. **Thibault Fiolet, Clin Microbiol Infect 2022;28:202**

Methods

Electronic searches for studies were conducted using Pubmed and Google scholar until 22nd September 2021 using the search terms "SARS-CoV-2", "COVID-19", "efficacy", "effectiveness", "neutralization assays", and "neutralization antibodies" in addition to the scientific or commercial names of the vaccines reported by WHO in phase III/IV. The ClinicalTrials.gov database was consulted using the terms "COVID-19" and "vaccine". BioRxiv and MedRxiv, regulatory drug agencies and pharmaceutical companies' websites were also consulted for unpublished results and additional information. Vaccines included in this review were approved in at least one country. CVnCoV and NVX-CoV2373 were in rolling review by the European Medicine Agency (EMA) and were included in this review.

Efficacy refers to the degree to which a vaccine prevents symptomatic or asymptomatic infection under controlled circumstances such as clinical trials. Effectiveness refers to how well the vaccine performs in the real world. In clinical trials, the main endpoint was the prevention of symptomatic COVID-19, whereas in observational studies endpoints were various and included asymptomatic SARS-CoV-2 infection, COVID-19, hospitalization or mortality.

Regarding seroneutralization assays, we extracted the age of the study population, dosage, and fold decrease in geometric mean titre for 50% neutralization compared to the SARS-CoV-2 reference strain for each vaccine and each SARS-CoV-2 variant when it was available.

Scoping Review

Randomised controlled trials evaluating artificial intelligence in clinical practice: a scoping review

Ryan Han, Julián N Acosta, Zahra Shakeri, John P A Ioannidis, Eric J Topol*, Pranav Rajpurkar*

This scoping review of randomised controlled trials on artificial intelligence (AI) in clinical practice reveals an expanding interest in AI across clinical specialties and locations. The USA and China are leading in the number of trials, with a focus on deep learning systems for medical imaging, particularly in gastroenterology and radiology. A majority of trials (70 [81%] of 86) report positive primary endpoints, primarily related to diagnostic yield or performance; however, the predominance of single-centre trials, little demographic reporting, and varying reports of operational efficiency raise concerns about the generalisability and practicality of these results. Despite the promising outcomes, considering the likelihood of publication bias and the need for more comprehensive research including multicentre trials, diverse outcome measures, and improved reporting standards is crucial. Future AI trials should prioritise patient-relevant outcomes to fully understand AI's true effects and limitations in health care.

Methods

Search strategy and selection criteria

We systematically searched PubMed, SCOPUS, CENTRAL, and the International Clinical Trials Registry Platform for relevant studies published between Jan 1, 2018, and Nov 14, 2023. This timeline was selected to coincide with the era when modern AI models began to play an important role in trials. We used free-text search terms such as "artificial intelligence", "clinician", and "clinical trial". The detailed search strategy can be found in the appendix (pp 3–7). Additionally, we manually scrutinised the references of pertinent publications to find more articles.

Our inclusion criteria were specific to RCTs that met the following conditions: the intervention incorporated a substantial AI component, which we defined as a non-linear computational model (ie, machine learning components including, but not limited to, decision trees, neural networks, etc); the intervention was integrated into clinical practice, thereby influencing a patient's health management by a clinical team; and the results were published as a full-text article in a peer-reviewed English-language journal. We excluded studies that evaluated linear risk scores, such as logistic regression, secondary studies, abstracts, and interventions that were not integrated into clinical practice. This scoping review follows the PRISMA extension for scoping reviews guidelines (appendix pp 8–9), and the protocol for this scoping review was registered with PROSPERO (CRD42022326955).[15]

Data analysis

To ensure the quality of our search results, we used Covidence Review software to screen publication titles and abstracts. Two independent investigators (RH and JNA) conducted the initial screening, followed by a full-text review of screened papers. Data extraction of eligible papers was done in Google Sheets by a single investigator and then verified by a second investigator (RH or JNA). Any discrepancies were resolved through discussion with a third reviewer (PR).

We extracted study-level information, including study location, participant characteristics, clinical task, primary endpoint, time efficiency endpoint, comparator, and result, as well as the type and origin of the AI used. Additionally, we classified studies by primary endpoint group (diagnostic yield or performance, clinical decision making, patient behaviour and symptoms, and care management), clinical area or speciality, and data modality used by the AI.

We did not attempt to contact study authors for additional or uncertain information. Due to the expected heterogeneity in tasks and endpoints, we did not conduct formal meta-analyses. Instead, we present simple descriptive statistics to provide an overview of the features of the eligible trials.

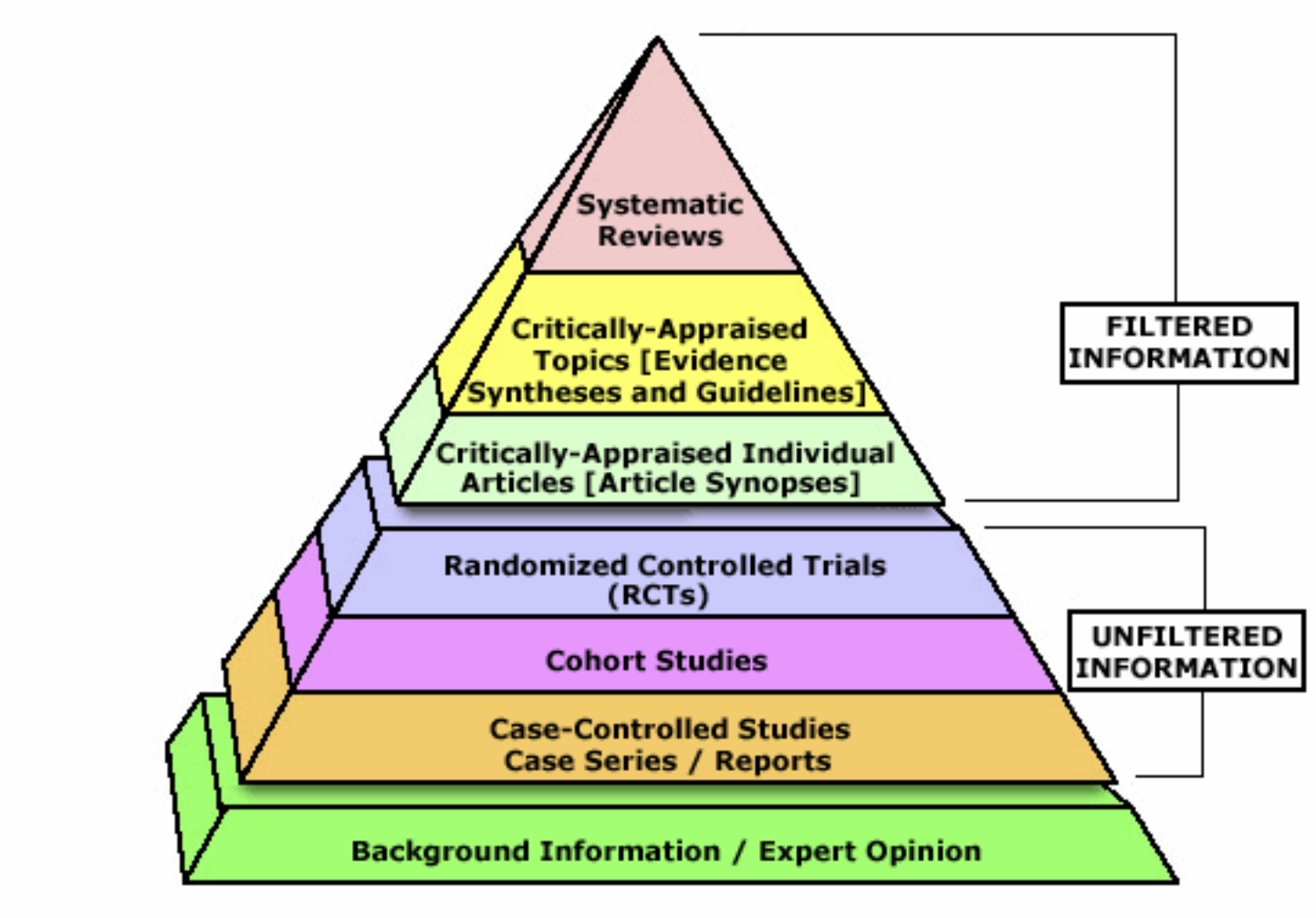
Definition

- A systematic review differs from traditional literature reviews by employing rigorous, explicit, and transparent methods.
- Key features include:
  - Use of explicit and transparent methods.
  - Conducted as a structured piece of research following standardized stages.
  - Designed to be accountable, replicable, and updateable.
  - Involvement of users to ensure relevance and utility.

Importance of Systematic Reviews

- Provide a more objective appraisal of evidence compared to narrative reviews.
- Help resolve uncertainty when original research, experts, and commentators disagree.
- Essential for determining whether new research is necessary and identifying specific questions for future studies.
- Minimize bias by adhering to basic principles, such as: Avoiding exclusion of relevant studies and using appropriate statistical methods for combining studies.

Evidence Pyramid



Systematic Review

Safety and effectiveness of vaccines against COVID-19 in children aged 5–11 years: a systematic review and meta-analysis

Vanessa Piechotta, Waldemar Siemens*, Iris Thielemann, Markus Toews, Judith Koch, Sabine Vygen-Bonnet, Kavita Kothari, Kathrin Grummich, Cordula Braun, Philipp Kapp, Valérie Labonté, Ole Wichmann, Joerg J Meerpohl†, Thomas Harder†*

Summary

Background To date, more than 761 million confirmed SARS-CoV-2 infections have been recorded globally, and more than half of all children are estimated to be seropositive. Despite high SARS-CoV-2 infection incidences, the rate of severe COVID-19 in children is low. We aimed to assess the safety and efficacy or effectiveness of COVID-19 vaccines approved in the EU for children aged 5–11 years.

Methods In this systematic review and meta-analysis, we included studies of any design identified through searching the COVID-19 L·OVE (living overview of evidence) platform up to Jan 23, 2023. We included studies with participants aged 5–11 years, with any COVID-19 vaccine approved by the European Medicines Agency—ie, mRNA vaccines BNT162b2 (Pfizer-BioNTech), BNT162b2 Bivalent (against original strain and omicron [BA.4 or BA.5]), mRNA-1273 (Moderna), or mRNA-1273.214 (against original strain and omicron BA.1). Efficacy and effectiveness outcomes were SARS-CoV-2 infection (PCR-confirmed or antigen-test confirmed), symptomatic COVID-19, hospital admission due to COVID-19, COVID-19-related mortality, multisystem inflammatory syndrome in children (MIS-C), and long-term effects of COVID-19 (long COVID or post-COVID-19 condition as defined by study investigators or per WHO definition). Safety outcomes of interest were serious adverse events, adverse events of special interest (eg, myocarditis), solicited local and systemic events, and unsolicited adverse events. We assessed risk of bias and rated the certainty of evidence (CoE) using the Grading of Recommendations Assessment, Development and Evaluation approach. This study was prospectively registered with PROSPERO, CRD42022306822.

Lancet Child Adolesc Health 2023; 7: 379–91

Published Online April 18, 2023 https://doi.org/10.1016/S2352-4642(23)00078-0

*Contributed equally as first authors

†Contributed equally as last authors

Immunisation Unit, Robert Koch Institute, Berlin, Germany (V Piechotta PhD, I Thielemann MSc, J Koch MD, S Vygen-Bonnet MD, O Wichmann MD, T Harder MD); **Institute for Evidence in Medicine, Medical Center–University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany** (W Siemens PhD, M Toews MSc,

When to Conduct a Review?

- Identifying Gaps in Literature:
  - If there is significant research but no substantive review, it might be time to synthesize that research into a review.
- Too Much Research, Too Many Reviews?
  - If there's already a large number of reviews on the topic, consider a review of reviews.
- Limited Research:
  - If there is little research on a topic, it might be better to focus on identifying research questions rather than writing a review.

* From Pautasso M. PLOS Comput Biol 2013; 9(7):e1003149.

Sum Up- Any Questions?

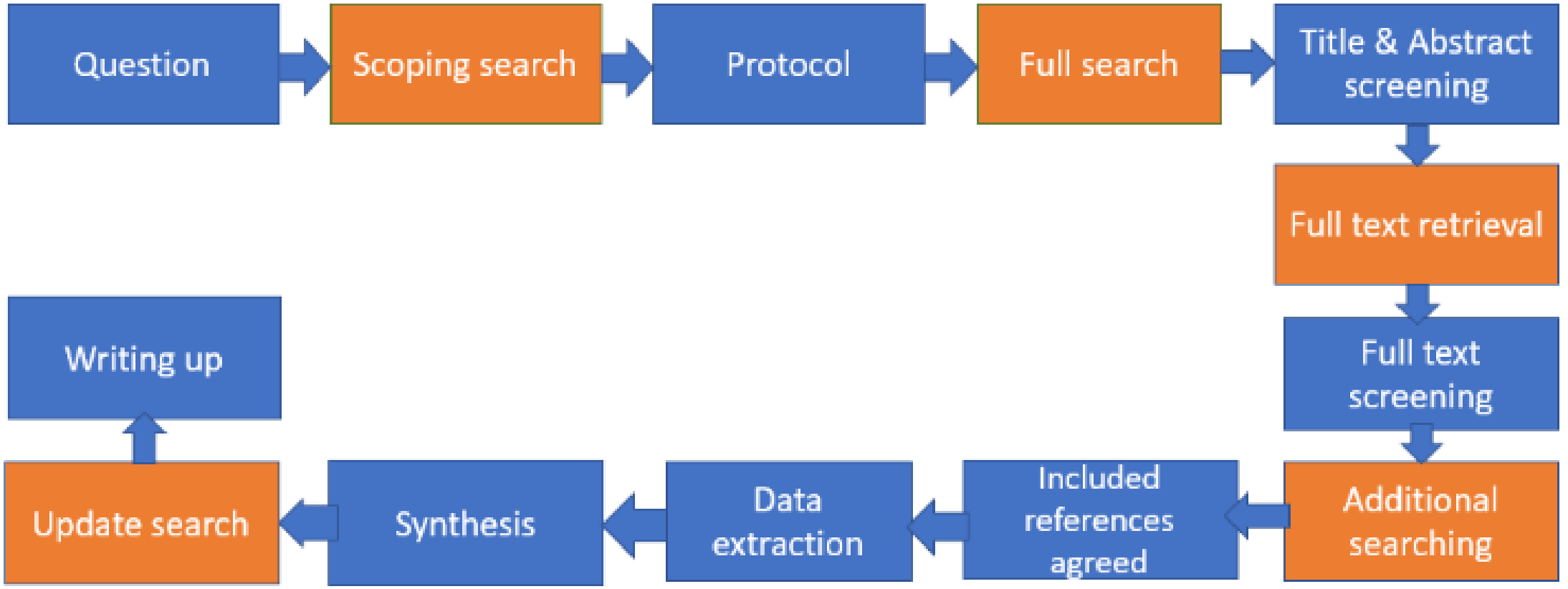
- History, importance, definition, and types of review articles, especially systematic review

Table 11.1: Defining characteristics of traditional literature reviews, scoping reviews and systematic reviews

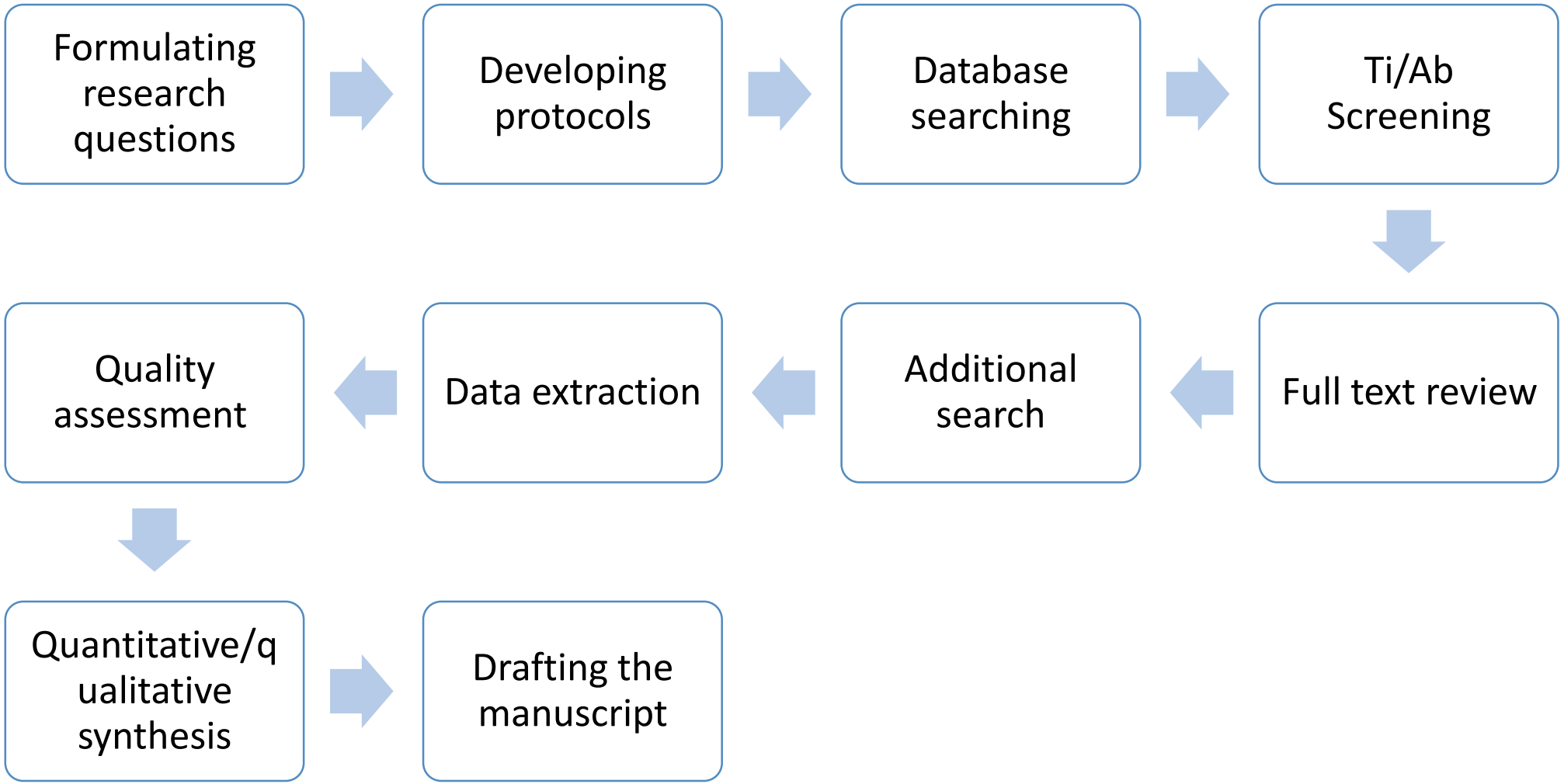
	Traditional Literature Reviews	Scoping reviews	Systematic reviews
A priori review protocol	No	Yes (some)	Yes
PROSPERO registration of the review protocol	No	No*	Yes
Explicit, transparent, peer reviewed search strategy	No	Yes	Yes
Standardized data extraction forms	No	Yes	Yes
Mandatory Critical Appraisal (Risk of Bias Assessment)	No	No**	Yes
Synthesis of findings from individual studies and the generation of 'summary' findings***	No	No	Yes

*Current situation; this may change in time, and we suggest registration/publication of scoping review protocols is critical. Examples of databases where scoping reviews may be registered are: is

Systematic Review Flowchart



Summary Steps of Systematic Review



Formulating Research Questions- PICOT

- PICOT is an acronym that stands for Population, Intervention, Control, Outcome, and Time (Type of Study).
  - Population (P): Define eligibility criteria, age, sex, settings, and data collection locations.
  - Intervention (I): What intervention or therapy are you considering? What hazards has your patient been exposed to? Type, duration, intensity, frequency?
  - Control (C): Provide detailed descriptions of control conditions for the intervention. No treatment, standard care, placebo, alternative treatment.
  - Outcome (O): What you want to measure (e.g., safety, efficacy, prevention)?
  - Time/Type of Study (T): How much time does it take to demonstrate the outcome(s)? RCT, case-control, cohort.
  - Statistical analysis or Study design (S): The statistical methods and tests will be used.

PICOT – Examples (Therapeutic)

- Does adding intravitreous steroids (I) to anti-VEGF therapy (C) reduce retinal thickness (O1) and/or improve visual acuity (O2) after 12 months (T) in patients with diabetic macular edema (P)?

PICOT – Examples (Diagnosis)

- In patients with suspected type 2 diabetes (P), is the A1C (I) compared with the fasting plasma glucose (C) more accurate in diagnosing type 2 diabetes (O)?

PICOT – Examples (Prognosis)

- In patients who have a family history of heart disease (P), how does choosing to participate in a nutrition program (I) compared with not choosing to participate in a nutrition program (C) influence healthy food consumption (O) over 6 months (T)?

PICOT – Examples (Etiology)

- Are children (P) who have sedentary lifestyles (I) compared with children without sedentary lifestyles (C) at higher risk of developing obesity (O) over a 6-month period (T)?

PICOT – Examples (Meaning)

- How do women (P) with postpartum depression (I) perceive their ability to function (O) during the postpartum period (T)?

PEO- Qualitative questions evaluating experiences, meaningfulness

Population	• who is the question focusing on or the population of interest?
Exposure	• what is the issue I'm interested in? • What is your population exposed to?
Outcome or themes	• what theme or outcome to examine? • What is the result of exposure in your population?

CHIP - questions for qualitative psychological research

Context	• What is the geographical and socio-cultural context?
How	• What is the research method of the study?
Issues	• What issues or experiences of the population are you investigating?
Population	• What population are you examining?

SPIDER - questions exploring experiences or meaningfulness

Sample	• What are the population or the group of people you are looking at?
Phenomenon of **I**nterest	• What is the issue or service you like to explore?
Design	• What type of study design are you following?
Evaluation	• How are you measuring the outcome?
Research Type	• Is it qualitative or quantitative or mixed methods?

Example: Exploring the Quality of Life for Saudi Patients Utilizing Dental Healthcare Services

Research Question	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
In hospitalized adult patients, does implementation of a nurse-led hand hygiene protocol compared to standard care reduce the incidence of hospital-acquired infections?	Hospitalized adults	Nurse-led hand hygiene protocol	Standard care (usual hand hygiene practices)	Incidence of hospital-acquired infections (e.g., MRSA, C. difficile)
Among type 2 diabetic patients, does a structured aerobic exercise program versus no structured exercise improve glycemic control?	Adults with type 2 diabetes	Structured aerobic exercise program	No structured exercise program	Change in HbA1c levels
In community-dwelling older adults, is daily probiotic supplementation compared to placebo effective in reducing the duration of acute respiratory infections?	Community-dwelling adults ≥65 years	Daily probiotic supplement	Placebo	Duration (days) of acute respiratory infection symptoms
For women with postpartum depression, does cognitive behavioral therapy delivered via telehealth versus in-person therapy lead to greater reduction in depression scores?	Postpartum women diagnosed with depression	Telehealth-delivered cognitive behavioral therapy	In-person cognitive behavioral therapy	Change in standardized depression scale scores (e.g., EPDS)
In patients undergoing total knee arthroplasty, does the use of continuous passive motion machines in addition to standard physiotherapy, compared to physiotherapy alone, improve postoperative range of motion?	Adults post–total knee arthroplasty	Continuous passive motion + standard physiotherapy	Standard physiotherapy alone	Degrees of knee flexion and extension at follow-up

Scoping Search

- No recent systematic review or systematic review protocol
  - Databases: PubMed and Cochrane Library
  - Search engines: Google Scholar
  - Protocol registries: PROSPERO
- Not too much or too many results
- What if there is a relevant systematic review
- What if there is a registered protocol

Formulating research questions- Sum Up- Any Questions?

- Different research question formulation methods
- Scoping search

PICOT, point by point

PICOT is an acronym for the following components of a clinical question

P	Patient population	What's the patient or group of patients of interest?
I	Intervention of interest	What's the main intervention or treatment you wish to consider?
C	Comparison intervention	Is there an alternative intervention or treatment to compare?
O	Outcome(s)	What's the clinical outcome(s)?
T	Time*	How much time does it take to demonstrate the clinical outcome(s)?

*Note that the time (T) component of the PICOT question isn't always required.

Question templates for asking PICOT questions

INTERVENTION

In_____(P), how does _____ (I) compared to _____ (C) affect _____(O) within_____(T)?

PROGNOSIS OR PREDICTION

In _____(P), how does _____ (I) compared to _____(C) influence/predict _____(O) over _____ (T)?

DIAGNOSIS OR DIAGNOSTIC TEST

In _____ (P) are/is _____(I) compared with _____(C) more accurate in diagnosing _____(O)?

ETIOLOGY

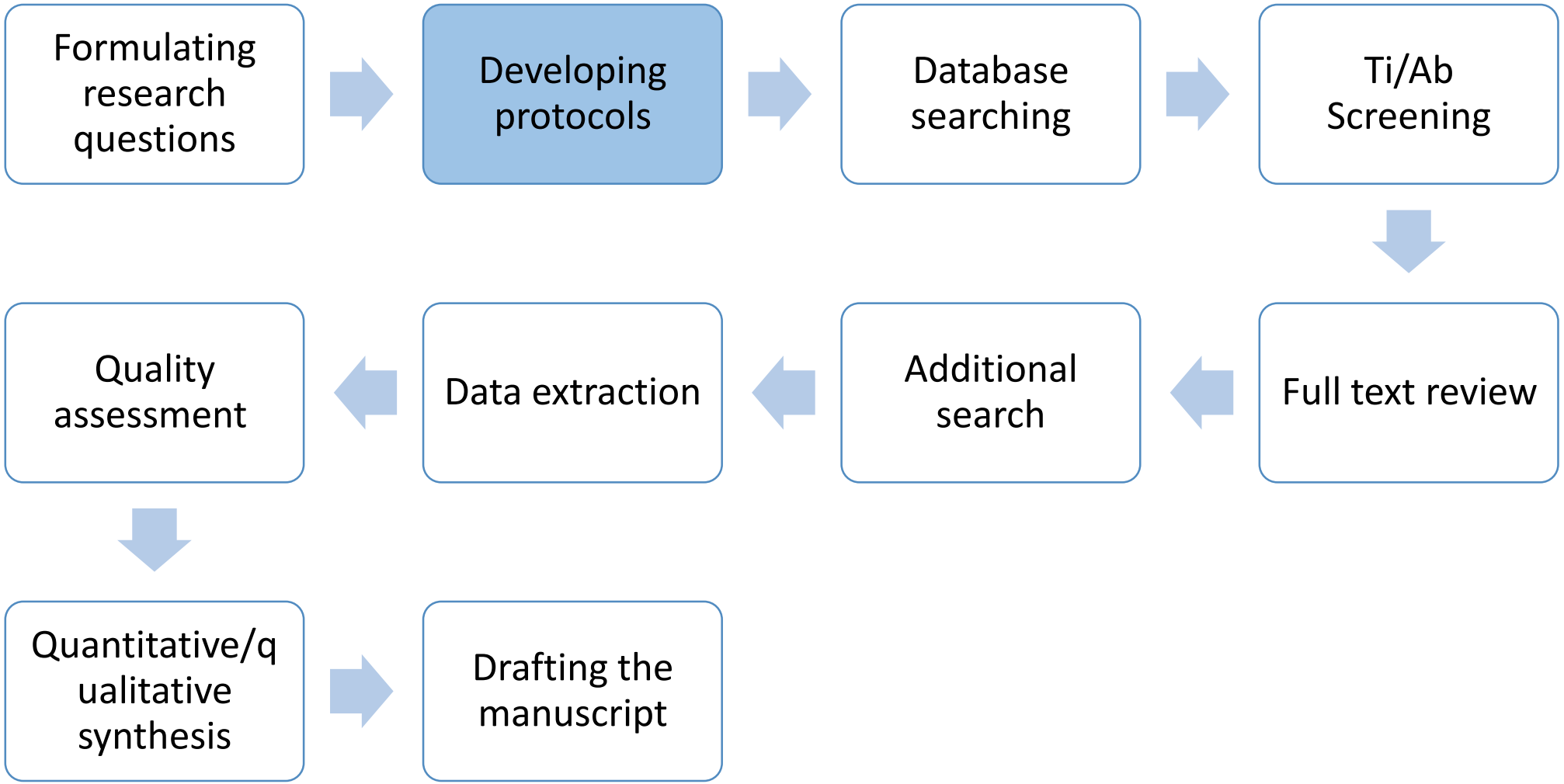
Are _____ (P), who have _____(I) compared with those without _____(C) at _____risk for/of _____(O) over _____(T)?

MEANING

How do _____ (P) with _____ (I) perceive _____ (O) during _____(T)?

Source: Melnyk BM, Fineout-Overholt E. *Evidence-Based Practice in Nursing and Healthcare: A Guide to Best Practice.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011. With permission.

Summary Steps of Systematic Review



Key Points on a Systematic Review Protocol

- **What is a Systematic Review Protocol?**
  - A protocol is a detailed document outlining the explicit plan for conducting a systematic review.
  - It includes the rationale, a priori methodology, and analytical approaches to be followed.
- **Purpose and Importance of a Systematic Review Protocol:**
  - **Specifies Methods in Advance:** Establishes a clear blueprint for the review process to maintain consistency and transparency.
  - **Saves Time and Effort:** Pre-planning reduces delays or complications during the review.
  - **Minimizes Risk of Bias:** Pre-defined methods limit subjective decisions that could skew results.

PROSPERO: International Prospective Register of Systematic Reviews

PROSPERO is an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health related outcome.

Registrations considerations for PROSPERO

Requirements for registration

- A full protocol should be ready before registering with PROSPERO
- Submissions must be made before data extraction commences (from October 2019)
- Registration forms must be complete.
- Submissions must be in English (search strategies and protocols attached to a record may be in any language).

PROSPERO does not accept:

- Systematic reviews without an outcome of clear relevance to the health of humans
- **Scoping reviews**
- Literature reviews that use a systematic search
- Systematic reviews assessing sports performance as an outcome
- Methodological reviews that assess ONLY the quality of reporting
- Systematic critical appraisals

Other considerations

- Systematic reviews of animal studies only are not eligible for registration in the section of PROSPERO dedicated to reviews of human studies. These should be registered in the section of PROSPERO for animal studies.
- Systematic reviews of in-vitro studies only are not eligible for registration on PROSPERO. We recommend registering such protocols elsewhere, for instance on Open Science Framework.

If you are in any doubt about the eligibility of your review, including the stage of progress please contact us by email using the details on the **contact page** for advice.

When to register your review

Do not register too early. Your systematic review protocol should be complete before you submit your registration request

Registering reviews that are never performed is unhelpful to the research community and may discredit the research team. You should therefore have the necessary resource in place to complete the review before you register your protocol (notification of award of research funding or firm commitment that author time is available for unfunded projects).

https://www.crd.york.ac.uk/PROSPERO/#guidancenotes

Registration steps

1. Review title.

This is a mandatory field

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Acronyms may be included in titles, but should not be used alone without expansion unless they are regarded as more usual than the expansion (e.g. HIV).

The title in this field must be in English. If the original title is in a different language the English version must be entered here, with the non-English version entered into the field labelled "Original Language Title".

If the final title of the review differs, this can be displayed in the Publication of Final Report Field.

Example: Systematic review and meta-analysis of recurrence and survival following pre- versus post-operative radiation in localized, resectable soft-tissue sarcoma.

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

Example: Revisión sistemática y meta-análisis de la recurrencia y la supervivencia tras la fase de radiación en comparación con post-operatorio en el sarcoma localizados resecables de tejido blando.

3. Anticipated or actual start date.

This is a mandatory field

Give the date when the systematic review commenced, or is expected to commence.

For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins.

A protocol can be deemed complete when it is approved by a funder or the person commissioning the review; when peer review is complete; when the protocol is published or when the authors decide that it is complete and they do not anticipate any major revisions to the design of the systematic review.

This field may be edited at any time. All edits to published records will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.

Example: 01 June 2011

4. Anticipated completion date.

This is a mandatory field

Give the date by which the review is expected to be completed. In the absence of an agreed contractual date, a realistic anticipated date for completion should be set. It can be modified should the schedule change. When this date is reached, the named contact will receive an automated email to ask them to provide an update on progress.

This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.

Example: 01 June 2011

5. Stage of review at time of this submission.

This is a mandatory field

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

Example: Preliminary searches ticked as completed, pilot of the study selection process ticked as started.

6. Named contact.

This is a mandatory field

The named contact acts as the guarantor for the accuracy of the information presented in the register record. This should be the lead reviewer or a representative of the review team. This person is also responsible for submitting details of any amendments while the review is ongoing and publication details after the review is completed. The named contact is the person to whom users of PROSPERO would send questions or comments.

This field is automatically populated from the named contact's signing in details. The named contact's name will be displayed in the public record.

Example: Dr Joseph Bloggs

N.B. To change the named contact for a published record, send details of the existing and new contact to **crd-register@york.ac.uk**

7. Named contact email.

This is a mandatory field

Give the electronic mail address of the named contact. This may be a generic email address to which the named contact has access.

This field is automatically populated from the named contact's joining details, but can be changed if required. The email address supplied here will be displayed in the public record.

Examples: joseph.bloggs@city.ac.uk or **research.secretary@city.ac.uk**

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information, i.e. personal home address

Give the full postal address for the named contact. (N.B. This field is automatically populated from the named contact's joining details.)

This address will be displayed in the public record. If you do not wish it to appear in the public record delete the content of this field.

Example: Alcuin B Block,University of York, York, YO10 5DD, UK

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
(N.B. This field is automatically populated from the named contact's joining details.)

This number will be displayed in the public record. If you do not wish it to appear in the public record delete the content of this field.

Example: +44 (0)10904 321040

10. Organisational affiliation of the review.

This is a mandatory field

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Example: Andalusian Agency for Health Technology Assessment (AETSA)

11. Review team members and their organisational affiliations.

This is a mandatory field

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**. Affiliation refers to groups or organisations to which review team members belong.

Review team members will be listed 'manuscript' style in the order entered in this list. The named contact will be automatically added to this field, but can be deleted if not a member of the review team. To place the named contact somewhere other than first in order, delete the automatic entry and enter members' details in the required order.

Membership of the review team and details of affiliations can be updated at any time.
All edits will appear in the record audit trail.

Example: Mr Joseph Bloggs, Centre for Reviews and Dissemination, University of York, UK. Dr Jane Smith, Department of Health Sciences, University of York, UK. Prof. Steven Jones, Centre for Health Statistics, Medical Research Centre, Canada.

12. Funding sources/sponsors.

This is a mandatory field

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Examples: NIHR HTA Programme (Project ref 09/13/02). The Terry Fox New Frontiers Program in Cancer (Ref 201006TFL). Funding provided by Amgen, Merck, Roche, and Sanofi-aventis.

13. Conflicts of interest.

This is a mandatory field

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review. The conflicts of interest listed should cover the review team as a whole, as well as individuals in the team.

Conflicts of interest arise when a team member or the team as a whole (e.g. because of the team's institution) has financial or personal relationships that may inappropriately influence (bias) their actions (such relationships are also known as dual commitments, competing interests, or competing loyalties).These relationships vary from being negligible to having great potential for influencing judgement. Not all relationships represent true conflict of interest.

On the other hand, the potential for conflict of interest can exist regardless of whether a person believes that the relationship affects his or her scientific judgement. Financial relationships (such as employment, consultancies, stock ownership, honoraria, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the review.

However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion. For the purposes of disclosure, the term "competing interest" should be considered synonymous with conflict of interest.[1]

Example: The lead reviewer (JB) has given talks on this topic at workshops, seminars, and conferences for which travel and accommodation has been paid for by the organisers. The other authors declare that they have no known conflicts of interest.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

Example: Dr Eric Porter, Oncologist, University Hospital, Brighton, UK. Clinical advisor.

15. Review question.

This is a mandatory field

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Example: How does pre-operative chemotherapy impact on survival of early stage non-small cell lung cancer compared to surgery alone?

16. Searches.

This is a mandatory field

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

The search strategy reported in systematic review protocols should:

- Name all sources that will be used to identify studies for the systematic review.

Sources include (but are not limited to) bibliographic databases, reference lists of eligible studies and review articles, key journals, conference proceedings, trials registers, Internet resources and contact with study investigators, experts and manufacturers.

Systematic reviews typically use more than one database. Examples of electronic bibliographic databases include MEDLINE, EMBASE, PsycINFO. Other database sources include The Cochrane Library, Health Technology Assessment Database, and Web of Science.

- Search dates (from and to)
- Restrictions on the search including language and publication period
- Whether searches will be re-run prior to the final analysis

It is considered good practice for searches to be re-run just before the final analyses and any further studies identified, retrieved for inclusion.

- Whether unpublished studies will be sought

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).
Alternatively, an electronic file could be supplied which will be linked to from the Register record. This will be made publicly available from the published record immediately, or it can be held in confidence until the review has been completed, at which time it will be made publicly available.

Example: http://www.biomedcentral.com/1756-0500/3/250

18. Condition or domain being studied.

This is a mandatory field

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Examples: Type 2 diabetes. Physical activity in children.

19. Participants/population.

This is a mandatory field

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Example:
Inclusion: Adults with schizophrenia (as diagnosed using any recognised diagnostic criteria).
Exclusion: Adolescents (under 18 years of age) and elderly people (over 70).

20. Intervention(s), exposure(s).

This is a mandatory field

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed. This is particularly important for reviews of complex interventions (interventions involving the interaction of several elements). If appropriate, an operational definition describing the content and delivery of the intervention should be given.

Ideally, an intervention should be reported in enough detail that others could reproduce it or assess its applicability to their own setting. The preferred format includes details of both inclusion and exclusion criteria.

For reviews of qualitative studies give details of the focus of the review.

Example: Population-level tobacco control interventions are defined as those applied to populations, groups, areas, jurisdictions or institutions with the aim of changing the social, physical, economic or legislative environment to make them less conducive to smoking. These are approaches that mainly rely on state or institutional control, either of a link in the supply chain or of smokers' behaviour in the presence of others.

Examples include tobacco crop substitution or diversification, removing subsidies on tobacco production, restricting trade in tobacco products, measures to prevent smuggling, measures to reduce illicit cross-border shopping, restricting advertising of tobacco products, restrictions on selling tobacco products to minors, mandatory health warning labels on tobacco products, increasing the price of tobacco products, restricting access to cigarette vending machines, restricting smoking in the workplace, and restricting smoking in public places. Such approaches could also form part of wider, multifaceted interventions in schools, workplaces or communities.[3]

21. Comparator(s)/control.

This is a mandatory field

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Control or comparison interventions should be described in as much detail as the intervention being reviewed. If the comparator is 'treatment as usual' or 'standard care', this should be described, with attention being paid to whether it is 'standard care' at the time that an eligible study was done, or at the time the review is done.

Systematic reviews of qualitative studies rarely have a comparator or control; stating 'Not applicable' is therefore acceptable.

Examples: Placebo. A group of hospital in-patients who were not exposed to the infectious agent.

22. Types of study to be included.

This is a mandatory field

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

If different study designs are needed for different parts of the review, this should be made clear. Where qualitative evidence will be incorporated in or alongside a review of quantitative data, this should be stated.

Example: We will include randomised trials to assess the beneficial effects of the treatments, and will supplement these with observational studies (including cohort and case–control studies) for the assessment of harms.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Include relevant details if these form part of the review's eligibility criteria but are not reported elsewhere in the PROSPERO record.

Examples: Studies in hospital accident and emergency departments. Research in low- and middle-income countries only will be included.

24. Main outcome(s).

This is a mandatory field

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

For systematic reviews of qualitative studies give details of what the review aims to achieve.

Examples: Change in depression score from baseline to the last available follow-up, measured using the Beck Depression Inventory. Five year progression-free survival (measured from randomisation). Establishing the barriers and facilitators to smoking cessation in pregnancy.

25. Additional outcome(s).

This is a mandatory field

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

Example: Apgar scores for the baby at 1 and 5 minutes after birth.

26. Data extraction (selection and coding).

This is a mandatory field

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Data extraction methods reported in systematic review protocols should include:

Study selection

- The number of reviewers applying eligibility criteria and selecting studies for inclusion in the systematic review (good practice suggests more than one individual) and how this will be done (e.g. whether two people will independently screen records for inclusion or whether one will screen and an other check decisions) and whether researchers will be blinded to each other's' decisions.
- How disagreements between individual judgements will be resolved
- The software system or mechanism for recording decisions

Data extraction

- List which data will be extracted from study documents, including information about study design and methodology, participant demographics and baseline characteristics, numbers of events or measures of effect (where applicable). Alternatively, state how this information will obtained from study investigators.
- The number of people extracting or checking received data (good practice suggests more than one individual) and how this will be done (e.g. whether two people will independently extract data or whether one will extract data and an other person check the extracted data).
- How disagreements between individual judgements will be resolved
- How missing data will be handled including whether study investigators will be contacted for unreported data or additional details.
- The means of recording data (e.g. in an excel spreadsheet, in a software system such as Eppi Reviewer)
- Another relevant detail that should be included is the software or tool, if any, that will be used for data extraction and management. An example of such a software tool is the Systematic Review Data Repository-Plus

27. Risk of bias (quality) assessment.

This is a mandatory field

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

Methods for assessing risk of bias reported in systematic review protocols should include:

- Which characteristics will be assessed (e.g. methods of randomisation, treatment allocation, blinding).
- Whether assessment will be done at study or outcome level
- The criteria used to assess internal validity, if formal a risk of bias assessment is planned (e.g. the Cochrane risk of bias tool, ROBINS, QUADAS).
- How the results of the assessment will inform data synthesis (where applicable).
- The number of reviewers that will be involved in the quality assessment
- How disagreements between reviewers judgements will be resolved

28. Strategy for data synthesis.

This is a mandatory field

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

Data synthesis methods reported in systematic review protocols should be specific about how they apply to the review and data in question and include:

- Criteria under which the data will be synthesised (e.g. the minimum number of studies or level of consistency required for synthesis)
- Which data will be synthesised including outcomes and summary effect measures (e.g. risk ratios for progression free survival at 2 years)
- The formal method of combining individual study data including, as applicable, information about statistical models that will be fitted (e.g. risk ratios for individual studies will be combined using a random effects meta-analysis) or methods of synthesising qualitative data.

29. Analysis of subgroups or subsets.

This is a mandatory field

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Planned 'subgroup' analysis or investigation of potential effect modifiers in reported in systematic review protocols should include:

- The rationale for the investigation (why are differences anticipated, or why is it important to look separately at different types of study or individual)
- Clear definitions of which types of study or individual will be included in each group (e.g. study design such as randomised/ non-randomised trial, intervention type such as high dose/low dose drug, setting such as hospital/ home care, participant characteristics such as male/female, stage III/stage IV tumour, <18 years/ ≥18 years)
- Details of the planned analytic approach (e.g. meta-regression, tests of interaction between groups, logistic regression using individual-level data). Where applicable this should include details of statistical models to be used.

30. Type and method of review.

This is a mandatory field

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

N.B. The information required here relates to the topic and outcome of the systematic review rather than the methods to be used. It is used to facilitate accurate searching of the database.

31. Language.

Select each country individually to add it to the list below, use the bin icon 🗑 to remove any added in error.

The entry will default to English if no other selection is made. For languages other than English, registrants are asked to indicate whether a summary or abstract will be made available in English.

Example: English, French.

32. Country.

This is a mandatory field

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Example: England, Canada.

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

Example: The title for this review and the review protocol are recorded in the Campbell Library as Project 27

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one. This may be to an external site such as a journal or organisational website. Alternatively an unpublished protocol may be deposited with CRD in pdf format. A link to this will be automatically added.

Example: Free C, Phillips G, Felix L, Galli L, Patel V, Edwards P. The effectiveness of M-health technologies for improving health and health services: a systematic review protocol. BMC Research Notes 2010, 3:250 doi:10.1186/1756-0500-3-250 **http://www.biomedcentral.com/1756-0500/3/250**.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences. Any knowledge transfer or implementation activities beyond publication of the final report that are planned should be included.

Example: In addition to producing a report for the funders of this review, which will be made available free of charge on their website, a paper will be submitted to a leading journal in this field. Furthermore, should the findings of the review warrant a change in practice, a one page summary report will be prepared and sent to lead clinicians and healthcare professionals in the National Health Service.

36. Keywords.

Give words or phrases that best describe the review. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

The addition of keywords is particularly important for non-effectiveness reviews. These records are likely to contain fewer relevant terms in other fields such as comparators and outcomes.

Information specialists at the Centre for Reviews and Dissemination (CRD) will assign MeSH terms, which will appear in the public record.

Example: Systematic review; meta-analysis; recurrence; survival; radiation; resectable; soft-tissue; sarcoma.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

Example: This review is an update of our earlier systematic review and economic model and is being undertaken in the light of the publication of significant new research which will assist in developing our model. The citation for the existing review is Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, Glasziou P, Bland M, Stirk L, Westwood M. A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions. *Health Technol Assess*. 2007;11(22):1-87.

38. Current review status.

This is a mandatory field

Review status should be updated when the review is completed and when it is published.

Select from the list below to indicate the current status of the review.

Use the free text box to provide an explanation of the status of the review.

Example: Discontinued: This review has been abandoned as we have been unable to secure adequate funding to proceed.

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

Example: This review is being undertaken as part of the planning for a randomised trial to compare all different types of radiotherapy for localised, resectable soft-tissue sarcoma.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint.

Give the full citation for the preprint or final report or publication of the systematic review, including the URL where available.

This field may also be used to record the availability of an un-published final report, summary results etc.

Example: Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC, Papadimas I. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. Eur J Endocrinol. 2010 Apr;162(4):643- 52. Epub 2009 Dec 2. **http://eje-online.org/cgi/content/full/162/4/643**

Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015)

- A guideline to help authors prepare protocols
- The PRISMA-P checklist is intended primarily for the preparation of protocols of systematic reviews and meta-analyses that summarize aggregate data from studies, particularly the evaluations of the effects of interventions.

https://www.prisma-statement.org/protocols

PRISMA-P

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

PRISMA-P

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.

Review Question- P and I

Methods

This systematic review protocol has been established according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 guideline (S1 Appendix) [16].

Eligibility criteria

Type of participants. Both men and women patients aged >18 years old with solid malignancies of any histologic type in any stage. The diagnosis of cancer should be established based on valid guidelines at the time of the studies. We will also include patients who have been administered combination therapies with BsAbs. Patients who have other comorbidities or metastatic cancers will also be included, while patients with benign tumors will be excluded. Patients with hematologic malignancies such as leukemia or lymphoma will be excluded.

Types of interventions. Administration of any BsAbs such as blinatumomab, catumaxomab, duligotuzumab, vanucizumab, cibisatamab, solitomab, istiratumab, navicixizumab, ertumaxomab, zenocutuzumab, flotetuzumab, faricimab, and emicizumab in interventional groups will be included. A list of all included BsAbs is available at S2 Appendix. The included clinical trials should have at least one arm receiving BsAb. We will also include patients who have been administered combination therapies with BsAbs. BsAb in pre-targeted radioimmunotherapy (PRIT) and also bispecific chimeric antigen receptors-T cell (CAR-T cell) therapy will be excluded.

Review Question- O

Types of outcome measures. Primary outcomes

1. Cumulative incidence of any grade AEs in each group
2. Cumulative incidence of severe grade AEs (grade 3–5) in each group
3. Overall survival (OS) (from baseline, i.e., first dose of intervention until death) in each group
4. Progression-free survival (PFS) according to RECIST (response evaluation criteria in solid tumors) 1.1 Criteria [17] (from baseline, i.e. first dose of intervention until disease progression or death) in each group
5. Duration of stable disease according to RECIST 1.1 Criteria [17] in each group
6. Objective response rate (ORR) as the proportion of participants with confirmed complete response (CR) or partial response (PR) according to RECIST 1.1 Criteria [17] in each group
7. Disease control rate as the proportion of participants with confirmed complete response (CR) or partial response (PR) or stable disease according to RECIST 1.1 Criteria [17] in each group

Secondary outcomes

1. Association between type of cancer and cumulative incidence of AEs
2. Association between type of cancer and cumulative incidence of severe AEs
3. Association between type of cancer and OS
4. Association between type of cancer and PFS
5. Association between type of cancer and ORR
6. Association between type of cancer and duration of stable disease
7. Association between type of cancer and disease control rate
8. Association between stage of cancer and cumulative incidence of AEs
9. Association between stage of cancer and cumulative incidence of severe AEs
10. Association between stage of cancer and OS
11. Association between stage of cancer and PFS
12. Association between stage of cancer and ORR
13. Association between stage of cancer and duration of stable disease
14. Association between stage of cancer and disease control rate

Review Question- T and Exclusion Criteria

Type of studies

Peer-reviewed clinical trial studies except for phase trials will be included. Only studies with survival or safety data available will be included in this systematic review.

Exclusion criteria

1. Studies on conditions other than malignant solid tumors
2. Patients with hematologic malignancies such as leukemia or lymphoma
3. Studies on participants aged $\leq$ 18 years old
4. Studies that did not assess treatment with BsAb
5. BsAb in PRIT and also bispecific CAR-T cell therapy
6. Studies in which survival measures such as overall response rate, PFS, and duration of stable disease or treatment-related AEs are not presented
7. Clinical trials without control group, phase clinical trials, case reports, pre-print articles, reviews, editorials, meta-analysis, commentary letters, conference proceedings, abstracts, trial protocols, re-analysis of previously published clinical trials, observational studies, retrospective studies, personal opinions, preclinical studies, and book chapters
8. Studies written in languages other than English

Identifying Research Evidence

Information sources

Electronic search. We will search the following sources:

1. PubMed
2. EMBASE
3. Scopus
4. Web of Science
5. Cochrane Central Register of Controlled Trials (CENTRAL)

Please see S3 Appendix for detailed search strategies. One month before submitting the final manuscript, we will perform an updated search on all mentioned databases. If we identify new studies for inclusion, we will evaluate these and incorporate findings in our review before submission of the final manuscript. We will implement no search filters or limitations on any field such as language, publication type, or time period in searching the electronic databases. We will send results of electronic searches to EndNote X9.0 (Clarivate Analytics, Philadelphia, PA, USA) reference manager, and duplicates will be identified and deleted by using it. Also, duplicates will be identified in the title/abstract screening process.

Searching other resources. We will search Clinical-Trials.gov (http://clinicaltrials.gov/) and metaRegister of controlled trials (http://www.isrctn.com/). Also, we will try to identify other potentially eligible trials by conducting backward and forward citation searches from included studies. We will contact corresponding authors for full-text articles, additional data, and unpublished trials.

Study Selection and Data Extraction

Data collection and analysis

Selection of studies. Two researches will independently evaluate the title and/or abstract of all retrieved articles based on inclusion and exclusion criteria. Full text of relevant and even potentially relevant articles will be found. Then after, these full texts will be investigated by two reviewers independently to determine the final included studies. Each study which reported abovementioned safety and/or efficacy measures that can be analyzed as continuous measures will be included in meta-analysis. Discrepancies in all stages will be resolved by discussion between the reviewers or consultant with a third review author. An adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart will be prepared (S4 Appendix) [16].

Data collection. Two authors will independently abstract characteristics of studies, participants, interventions, and outcomes including first author, year of publication, digital object identifier (DOI) of the article, phase of clinical trial, study design (e.g., parallel or cross-over), funding sources, number of arms, total number of participants, number of participants in each group, mean/median/range of age in each group, number of patients with each gender in each group, number of patients with each cancer type in each group, number of patients with each stage of cancer in each group, number of patients with each race/ethnicity in each group, number of participants completed the study in each group, median follow-up in each group, type of BsAb and its targets, type of control medication, dose and schedule of BsAb and control medication, total number of AEs and irAEs in each group, total number of severe AEs and severe irAEs in each group, total number of DLTs in each group, OS in each group, PFS in each group, ORR in each group, duration of stable disease in each group, and disease control rate in each group [18]. Disagreements between reviewers will be solved by discussion or consultation with a third author. Relevant missing information will be requested from corresponding authors via emailing them.

Data Synthesis

Data synthesis

Statistical analysis. Dichotomous data will be expressed as risk ratios (RRs) with 95% confidence intervals (CIs), including cumulative incidence of any grade of AEs and irAEs, severe AEs and severe irAEs, DLTs, ORR, and disease control rate. Standardized/raw mean differences (MD) with 95% CIs will be expressed for continuous data, including OS, PFS, and duration of stable disease. STATA 16 (STATA Corp LLC, TX) software will be used for meta-analysis if applicable. In order to find the source of heterogeneity, we will implement subgroup analysis based on sex, type of cancer, and stage of cancer. Also, meta-regression will be used for age. In addition, the metaprop command of STATA will be used to calculate the frequency of AEs in intervention and control groups.

Dealing with zero cells. We will add continuity correction of 0.5 to cells of each one of intervention or control arms that are zero [24]. Furthermore, we will perform sensitivity analysis to compare the effects of this type of continuity correction [25] because some studies have criticized this method due to its effects on meta-analysis results [26, 27].

Assessment of heterogeneity. I^2 index for heterogeneity will be calculated by Q statistics tests for assessment of heterogeneity [28]. According to the Cochrane Handbook for Systematic Reviews of Interventions, the I^2 level more than 40% is considered significant [28]. As a result, random-effect model meta-analysis will be undertaken if the heterogeneity is more than 40% [18]. Otherwise, fixed-effect meta-analysis will be used.

Sensitivity analysis. We will undertake sensitivity analysis to evaluate the effects of continuity correction and roles of funding sources on the effect size when applicable.

Confidence in cumulative evidence. We will use the Grading of Recommendations Assessment Development and Evaluation (GRADE) instrument in order to assess the quality of evidence as four levels of high quality, moderate quality, low quality, and very low quality [29].

PLOS ONE

STUDY PROTOCOL

Clinical safety and efficacy of bispecific antibody in the treatment of solid tumors: A protocol for a systematic review

Seyed Aria Nejadghaderi[1,2☯], **Maryam Balibegloo**[1,2,3☯], **Amene Saghazadeh**[1,4], **Nima Rezaei**[3,4,5*]

1 Systematic Review and Meta-Analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran, **2** Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran, **3** Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran, **4** Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences (TUMS), Tehran, Iran, **5** Department of Immunology, School of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran

☯ These authors contributed equally to this work.
* nimarezaei.usern@gmail.com, rezaei_nima@tums.ac.ir

OPEN ACCESS

Citation: Nejadghaderi SA, Balibegloo M, Saghazadeh A, Rezaei N (2022) Clinical safety and efficacy of bispecific antibody in the treatment of solid tumors: A protocol for a systematic review. PLoS ONE 17(7): e0271506. https://doi.org/10.1371/journal.pone.0271506

Editor: Hugh Cowley, Public Library of Science, UNITED KINGDOM

Received: June 26, 2021

Accepted: July 1, 2022

Published: July 18, 2022

Data Availability Statement: No datasets were generated or analysed during the current study. All relevant data from this study will be made available upon study completion.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: DALYs, Disability-adjusted life years; ICIs, Immune checkpoint inhibitors; CTLA-4,

Abstract

Background

Cancers are among the most common causes of mortality and morbidity. Recently, bispecific antibodies (BsAbs) have been used for cancer treatment. The aim of this systematic review and meta-analysis will be to determine the safety and efficacy of BsAbs in the treatment of solid tumors.

Methods

We will search five electronic databases, PubMed, EMBASE, Scopus, Web of Science, and CENTRAL, in addition to Clinical-Trials.gov and metaRegister of controlled trials and backward and forward citation searching of included studies. Eligible studies will be controlled clinical trials evaluating safety and/or efficacy of BsAbs in adult patients with solid tumors. The primary outcomes will be the incidence of safety and efficacy measures. Title and/or abstract screening, full text reviewing, data collection, and quality assessment will be done by two reviewers. We will use The Cochrane Collaboration's risk of bias tool 2 (RoB2) to assess the quality of included studies. If I-square heterogeneity was greater than 40%, we will implement random effect model. Subgroup analysis and meta-regression will be undertaken if applicable. The metaprop command of STATA will be used to calculate frequency of AEs. Funnel plot, Egger's and Peter's tests will be utilized to evaluate publication bias in case of including at least ten studies. We will use sensitivity analysis to evaluate the effects of funding sources and continuity correction on effects size.

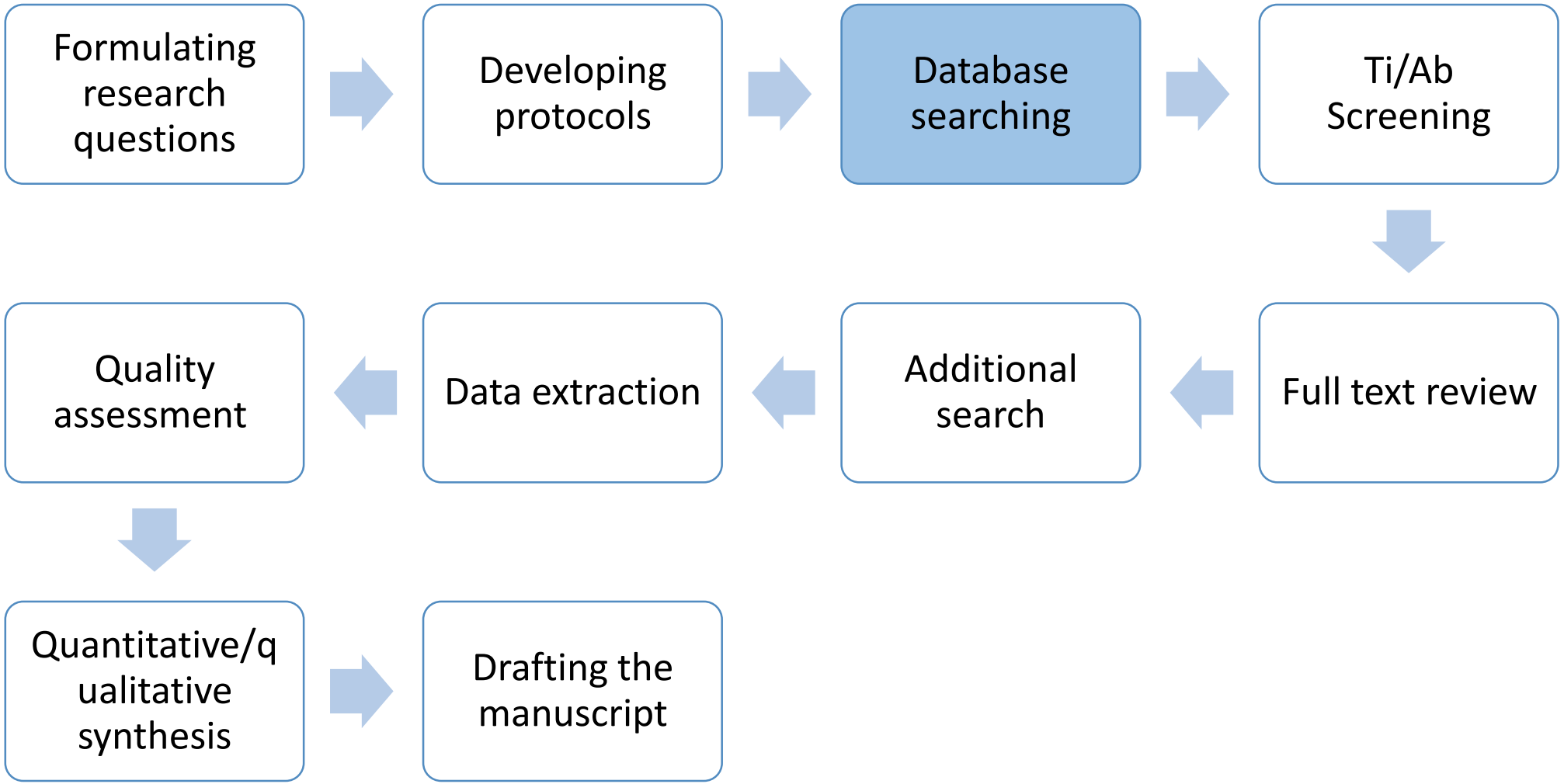
Conclusions

The findings of the present study will provide information on safety and efficacy of BsAbs for physicians and researchers in the management of solid tumors.

Sum Up- Any Questions?

- Protocol registries: PROSPERO
- Protocol items
- PRISMA-P
- Possibility of publishing protocols

Summary Steps of Systematic Review



Steps for Designing a Search Strategy

- **Systematic Search of Databases:** Use bibliographic databases (e.g., PubMed or Scopus).
- **Look for Existing Reviews:** Identify and review existing systematic reviews in your topic area.
- **Existing Search Strategies:** Modify pre-existing search strategies from similar studies or reviews.
- **Use Keywords and Controlled Vocabulary:** Include a combination of keywords and database-specific terms, such as MeSH headings in MEDLINE, to enhance search precision.

Systematic Review Search Template

Develop table for key concepts in research question (e.g. according to PICO model) and find search terms for each concept – identify controlled vocabulary and free text terms to create your searches; join all terms within each concept with **OR**

	Concept 1	**Concept 2**	**Concept 3**	**Concept 4**
Key concepts				
Controlled vocabulary terms / Subject terms (MeSH terms, Emtree terms) *Consider: explode, major headings, subheadings*				
Free text terms / natural language terms (synonyms, UK/US terminology, medical/laymen's terms, acronyms/abbreviations, drug brands, more narrow search terms) *Consider: phrase searching, proximity operators, truncation, wildcards, field qualification (e.g. textword)*				
	Search 1 result (#1) =	Search 2 result (#2) =	Search 3 result (#3) =	Search 4 result (#4) =

Now you are confident you have found all relevant information for each concept in your topic, join them together using **AND**. In most databases you do this in your search history. Your search may be #1 AND #2 AND #3 AND #4

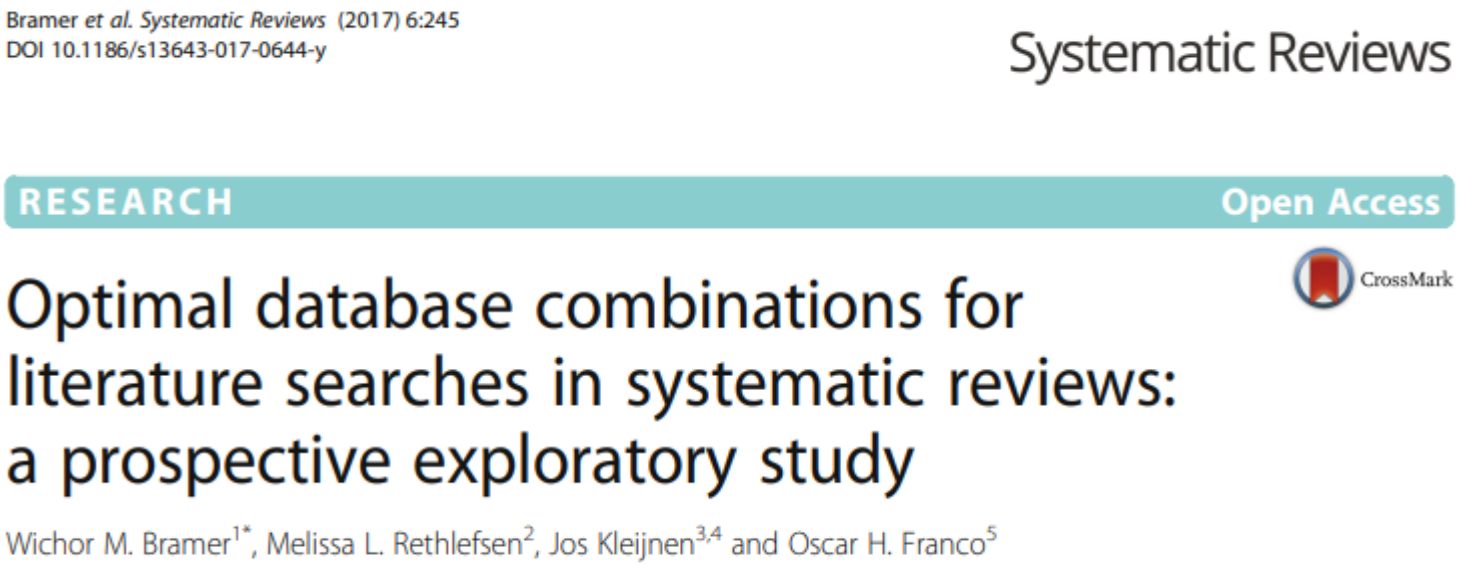
Systematic Review Search Example

Database (Search date)	Step	Search Strategy	Number of Results
PubMed (8.4.2022)	#1	"cannabidiol"[mh] OR "cannabidiol"[tiab] OR "CBD"[tiab] OR "epidiolex"[tiab] OR "epidyolex"[tiab]	11,078
	#2	"epilepsy"[mh] OR "epileps*"[tiab] OR "epileptic" OR "seizures"[mh] OR "seizur*"[tiab]	252,693
	#3	#1 AND #2	808
Scopus (8.4.2022)	#1	TITLE-ABS-KEY ("cannabidiol" OR "CBD" OR "epidiolex" OR "epidyolex")	21,744
	#2	TITLE-ABS-KEY ("epileps*" OR "eplileptic" OR "seizur*")	361,580
	#3	#1 AND #2	1,456
Web of Science (8.4.2022)	#1	TS=("cannabidiol" OR "CBD" OR "epidiolex" OR "epidyolex")	16,676
	#2	TS=("epileps*" OR "epileptic" OR "seizur*")	247,805
	#3	#1 AND #2	1,014
Google Scholar (8.18.2022)		(("cannabidiol" OR "CBD" OR "epidiolex" OR "epidyolex") AND ("epilepsy" OR "epilepsies" OR "espilepsia" OR "epileptic" OR "seizure" OR "seizures"))	27,600

Fazlollahi A, Zahmatyar M, ZareDini M, Golabi B, Nejadghaderi SA, Sullman MJM, Gharagozli K, Kolahi AA, Safiri S. **Adverse Events of Cannabidiol Use in Patients With Epilepsy: A Systematic Review and Meta-analysis.** JAMA Netw Open. 2023 Apr 3;6(4):e239126. doi: 10.1001/jamanetworkopen.2023.9126.

Which databases?

- The Cochrane Central Register of Controlled Trials (**CENTRAL**) and **MEDLINE**, together with **Embase** (if access to Embase is available to the review team), should be searched for all Cochrane Reviews.
- Optimal searches in systematic reviews should search **at least Embase, MEDLINE, Web of Science, and Google Scholar** as a minimum requirement to guarantee adequate and efficient coverage.


Bramer *et al. Systematic Reviews* (2017) 6:245
DOI 10.1186/s13643-017-0644-y

Systematic Reviews

RESEARCH Open Access

Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study

Wichor M. Bramer[1*], Melissa L. Rethlefsen[2], Jos Kleijnen[3,4] and Oscar H. Franco[5]

Evaluating and Revising Search Results

- Assess the number of results retrieved from each search.
- Identify which search terms or strategies produced the highest number of results.
- Evaluate the retrieved papers for:
  - Known relevant papers.
  - Potentially relevant new papers.
  - Irrelevant papers.
- Revise if:
  - The search had too many or too few results.
  - The strategy fails to retrieve papers you know are relevant.

Sum Up- Any Questions?

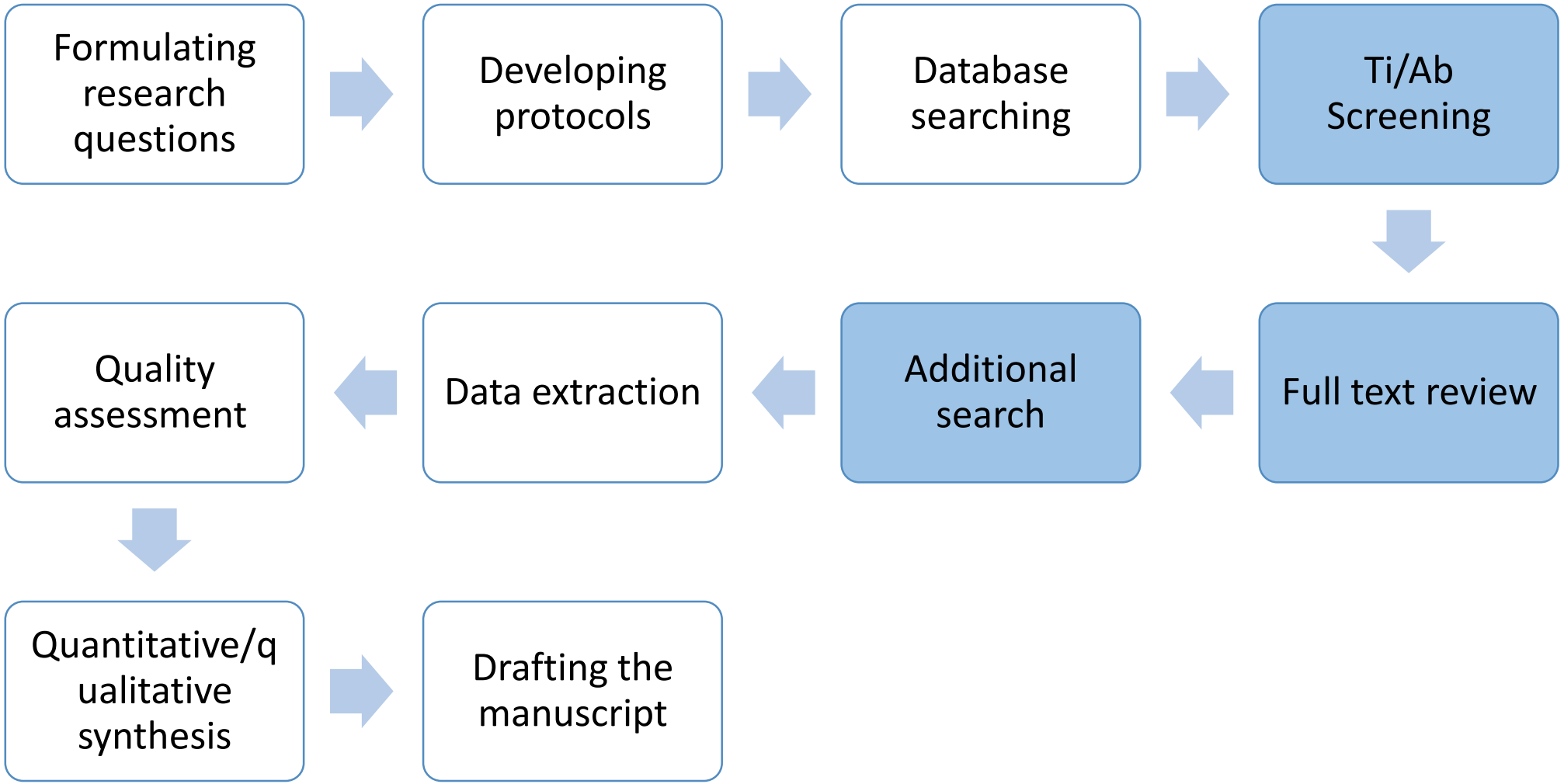
- Tips for search strategy design
- Template for search strategy

Checklist for Reviewing Search Strategies

1. Translation of the research question into search concepts	Comments
• Does the search strategy match the research question/PICO? • Are the search concepts clear? • Are there too many or too few PICO elements included? • Are the search concepts too broad or too narrow? • Does the search retrieve too many or too few records? • Are unconventional or complex strategies explained?	
2. Boolean operators	
• Are Boolean and proximity operators used correctly? • Is the use of nesting with brackets appropriate and effective for the search? • If NOT is used, is this likely to result in any unintended exclusions?	
3. Proximity operators	
• Could the search be improved by using proximity operators (eg. adj, near) instead of AND? • Is the width of proximity operators suitable (eg. adj5 as opposed to adj3 or adj10)?	
4. Subject headings	
• Are the subject headings used relevant? • Are any additional subject headings missing? • Are any subject headings too broad/too narrow? • Are subject headings exploded where necessary and vice-versa? Are all exploded headings relevant? • Are subheadings used appropriately/missing?	
5. Text word searching	
• Have all relevant synonyms, related terms and antonyms been searched? • Are text word searches included appropriate – eg. too broad, too narrow? • Is truncation used appropriately? • Are acronyms or abbreviations used appropriately? • Have the appropriate fields been searched (eg. tw, mp)?	
6. Spelling	
• Are there any spelling errors? • Are alternate spellings of words included?	
7. Search limits	
• Are limits used appropriately and are they relevant given the research question? • Are any potentially helpful limits missing?	
8. Search line numbers	
• Has each line number and combination of line numbers need checked?	
9. Strategy adapted to each database	
• Have all relevant databases been identified? • Has the search strategy been adapted for each database?	
10. Additional Comments	

This checklist is based on the *CADTH Methods and Guidelines PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E)* - January 2016. www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf

Summary Steps of Systematic Review



Study Selection

- Purpose:
  - After completing the search strategy, decide which studies to include and exclude in the review.
- Volume of Studies:
  - Expect to identify more studies than necessary for detailed review.
- Inclusion Criteria:
  - Create and document specific inclusion criteria before conducting the search to streamline the selection process and reduce bias.
  - Define these criteria based on the study's relevance to the research question, such as population, intervention, outcome, or methodology.

Screening, Full Text Review, and Discrepancy Example

All articles identified through the electronic and manual searches were exported to EndNote, version 20 (Clarivate), and any duplicates were removed. Two authors (A.F. and M. ZareDini) independently screened the title and abstract of the articles and excluded those that were irrelevant. In the next step, the same 2 authors reviewed the full texts of the remaining articles. Any discrepancies were resolved by discussion or consultation with other authors.

Studies were included if they were randomized clinical trials (RCTs) investigating at least 1 AE associated with CBD use in patients with epilepsy. All classifications of epilepsy were included, with no age restriction. Studies were excluded if they were not RCTs, did not consider the AEs of CBD, or included patients with diseases other than epilepsy.

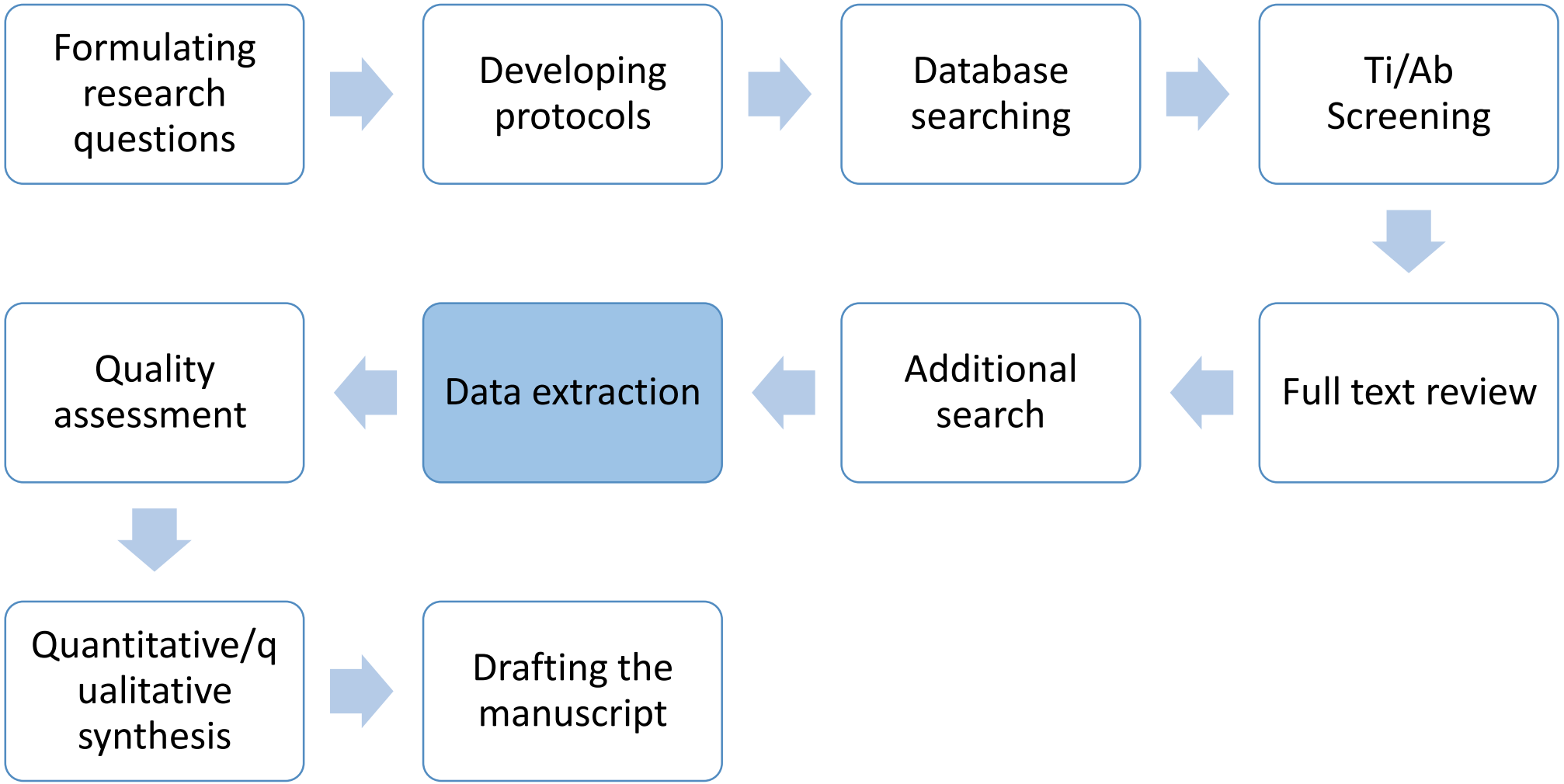
Additional Search

- Searching Grey Literature:
  - Non-traditional sources like reports, dissertations, theses, and conference abstracts.
  - Google Scholar (the first 100-300 results)
- Searching Within Other Reviews:
  - Review previous systematic reviews on the topic for studies and references.
- Backward and Forward Citation Search

Sum Up- Any Questions?

- Ti/ab screening
- Full text retrieval and review
- Additional search
  - Google Scholar
  - Backward and forward citation search

Summary Steps of Systematic Review



Data Extraction – Purpose

- Data extraction in a systematic review ensures that relevant information from each study is **systematically collected for analysis**.
- A structured process minimizes **errors**, reduces **bias**, and ensures **consistency** across studies.
- Usually performed by two independent reviewers

Data Extraction – Items

- **General Information**
- **Data Extractors:** Record the names of individuals performing the extraction and the date of extraction.
- **Identification Features:** Include citation details, study ID, and other identifiers for easy traceability.
- **Study Methods**
- **Design:** Specify the study type (e.g., randomized trials, observational studies) and key design elements such as parallel or crossover.
- **Recruitment and Sampling:** Detail recruitment strategies, sampling methods, and the number of sites (if multicenter).
- **Timeline:** Note the enrollment start and end dates, as well as the length of follow-up.

Data Extraction – Items Cont.

- **Randomization:** For randomized trials, include details on random sequence generation, allocation concealment, and masking. For non-randomized studies, describe methods to control for biases and confounding.
- **Missing Data:** Record methods used to address missing data, such as imputation or sensitivity analyses.
- **Statistical Analysis:** Document the statistical methods, unit of analysis, and any covariates included in models.
- **Bias and Funding:** Include details on funding sources, authors' financial relationships, and potential conflicts of interest.
- **Participants**
- **Setting:** Report the geographic region and country where participants were recruited.
- **Eligibility Criteria:** Describe participant inclusion and exclusion criteria.
- **Baseline Characteristics:** Provide details such as age, sex, socioeconomic status, and comorbidities.

Data Extraction – Items Cont.

- **Intervention and Comparators**
- **Intervention Details:** Describe intervention components, dosage, frequency, duration, and route of administration with enough detail for replication.
- **Comparator Details:** Clearly define control groups, whether they involve no intervention, placebo, or usual care.
- **Implementation Factors:** Record factors influencing the delivery of interventions, such as staff qualifications and equipment requirements.
- **Co-interventions and Integrity:** Note any additional treatments participants received and assess whether the intervention was delivered as planned.

Data Extraction – Items Cont.

- **Outcomes**
- **Pre-Specified Outcomes:** Confirm whether outcomes were measured and reported.
- **Measurement Tools:** Specify tools or instruments used, including scales, thresholds, and whether higher or lower scores are favorable.
- **Timing:** Document when outcomes were assessed, such as pre- or post-intervention periods.
- **Adverse Events:** Note whether adverse events were systematically or non-systematically collected.

Data Extraction – Items Cont.

- **Results**
- **Group-Level Data:** Extract summary statistics (e.g., means, standard deviations, proportions) for each group.
- **Effect Estimates:** Record effect sizes (e.g., odds ratios, mean differences) and their precision (e.g., confidence intervals).
- **Subgroups:** For subgroup analyses, collect corresponding data by participant characteristics.
- **Miscellaneous**
- **Authors' Conclusions:** Summarize key points made by the study authors.
- **References:** Note references to other relevant studies cited within the paper.
- **Comments:** Include any notes or clarifications from the authors or review team.

Data Extraction Example

Data Extraction

Data extraction was conducted using previously designed Microsoft Office Excel forms (Microsoft Corp). Two reviewers (M. Zahmatyar and B.G.) independently extracted the following information from each included study: (1) the basic information about the study, including title, first author's name, country, and publication date; (2) the characteristics of the participants, including study population, sample size, age, sex, type of epilepsy, and medications used for the treatment of epilepsy; and (3) the total number and severity of all-cause and treatment-related AEs observed in both the experimental and control groups as well as the total number of AEs resulting in discontinuation or dose reduction in both groups. Any disagreements were settled through discussion between the 2 reviewers or by conferring with a third reviewer (A.F.). Negative clinical events that developed in study participants after administration of CBD or placebo were considered to be AEs. We categorized the AEs according to the Common Terminology Criteria for Adverse Events, version 5.0.[15]

Data Transformation and Handling

- Statistical variable conversion: Meta-Analysis Accelerator (https://meta-converter.com/)
- Graphs: PlotDigitizer

Abbas *et al. BMC Medical Research Methodology* (2024) 24:243
https://doi.org/10.1186/s12874-024-02356-6

BMC Medical Research Methodology

SOFTWARE Open Access

Meta-analysis accelerator: a comprehensive tool for statistical data conversion in systematic reviews with meta-analysis

Abdallah Abbas[1*], Mahmoud Tarek Hefnawy[2] and Ahmed Negida[2,3]

Abstract

Background Systematic review with meta-analysis integrates findings from multiple studies, offering robust conclusions on treatment effects and guiding evidence-based medicine. However, the process is often hampered by challenges such as inconsistent data reporting, complex calculations, and time constraints. Researchers must convert various statistical measures into a common format, which can be error-prone and labor-intensive without the right tools.

Implementation Meta-Analysis Accelerator was developed to address these challenges. The tool offers 21 different statistical conversions, including median & interquartile range (IQR) to mean & standard deviation (SD), standard error of the mean (SEM) to SD, and confidence interval (CI) to SD for one and two groups, among others. It is designed with an intuitive interface, ensuring that users can navigate the tool easily and perform conversions accurately and efficiently. The website structure includes a home page, conversion page, request a conversion feature, about page, articles page, and privacy policy page. This comprehensive design supports the tool's primary goal of simplifying the meta-analysis process.

Data Extraction Tools

- **1. Excel**
- **Flexibility:** Design custom spreadsheets for data extraction.
- **Best For:** Small-scale projects and manual processes.
- **2. Covidence**
- **Purpose-Built Software:** Streamlines screening, data extraction, and management.
- **Features:** Customizable tables and easy export of extracted data.
- **Best For:** Teams requiring seamless collaboration.
- **3. RevMan**
- **Cochrane's Tool:** Software for data extraction and meta-analysis.
- **Features:** Guided templates for data analysis and synthesis.
- **Best For:** Reviews adhering to Cochrane methodologies.
- **4. DistillerSR**
- **Automation-Powered:** Supports project-specific forms, AI-assisted extraction, and analysis.
- **Best For:** Large, complex reviews requiring scalability.

Data Extraction Tools - Excel

NO	Study ID	Study Title	First Author Name	Study design (Parallel - Cross-over -	Publication year	Country	DOI/URL
1	Devinsky, 2017	Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome	Orrin Devinsky	Parallel	May 25, 2017	Multinational (United States and Europe)	10.1056/NEJMoa1611618
2	De						
3	De						

Study ID

Characteristics of the study

Phase of trial (Pilot - 1 - 2 - 3 - 4 -	Sampling setting (Community - Primary care - Inpatient -	Blinding (Non - Single - Double -	ITT analysis (Yes - No -	Sample Size	No of patients that completed the treatment	Study Population	Quality Assessment
LMC	Unclear	Double	Yes	120 Cannabidiol, 20: 61 Placebo:59	108	177 Children and young adults	Some concerns
3							

Demographic Features

Race/Ethnicity/Region (Caucasian - Hispanic - African - East Asian - Middle-Eastern - Mixed - Other - Unclear)	Male (Z)	Male in intervention (Z)	Female (Z)	Female in intervention (Z)	BMI Mean (SD)	Age group (years)	Age Range (year)	Median (year)	Mean Age ± SD
Multinational United States (Treatment (Cannabidiol): 35; 57Z / Control (Placebo): 37; 63Z / Total: 72; 60Z) Rest of world (Treatment (Cannabidiol): 26; 43Z / Control (Placebo): 22; 37Z / Total: 48; 40Z)	Treatment (Cannabidiol): 35; 57Z Control (Placebo): 27; 46Z Total: 62; 52Z	35; 57Z	Treatment (Cannabidiol): 26; 43Z Control (Placebo): 32; 54Z Total: 58; 48Z	26; 43Z	CBD: 18.3±4.5 Placebo: 19.1±4.7 Total: 18.7±4.6	N/A	Treatment (Cannabidiol): 2.5-18.0 yr Control (Placebo): 2.3-18.4 yr Total: 2.3-18.4 yr	Treatment (Cannabidiol): 9.1 yr Control (Placebo): 9.2 yr Total: 9.2 yr	Treatment (Cannal 9.7±4.7 yr Control (Placebo): 9 Total: 9.8±4.8
Multicenter The majority of patients were white and were from the United States. White/Caucasian (Treatment (Cannabidiol, 20): 67; 88.2Z / Treatment (Cannabidiol, 10): 62; 84.9Z / Placebo: 69; 90.8Z) Other (Treatment (Cannabidiol, 20): 9; 11.8Z / Treatment (Cannabidiol, 10): 11; 15.1Z / Placebo: 7; 9.2Z) USA (Treatment (Cannabidiol, 20): 59; 77.6Z / Treatment (Cannabidiol, 10): 60; 82.2Z / Placebo: 62; 81.6Z) Rest of World (Treatment (Cannabidiol, 2017; 22.4Z / Treatment (Cannabidiol, 10): 13; 17.8Z / Placebo: 14; 18.4Z)	Treatment (Cannabidiol, 20): 45; 59Z Treatment (Cannabidiol, 10): 40; 55Z Placebo: 44; 58Z Total: 129; 57Z	85; 57Z	Treatment (Cannabidiol, 20): 31; 41Z Treatment (Cannabidiol, 10): 33; 45Z Placebo: 32; 42Z Total: 96; 43Z	64; 43Z		N/A	Treatment (Cannabidiol, 20): 2.6-48.0 yr Treatment (Cannabidiol, 10): 2.6-42.6 yr Placebo: 2.6-43.4 yr	N/A	Treatment (Cannabic 16.0±10.8 yr Treatment (Cannabic 15.4±9.5 yr Placebo: 15.3±9

Data Extraction Tools - Excel

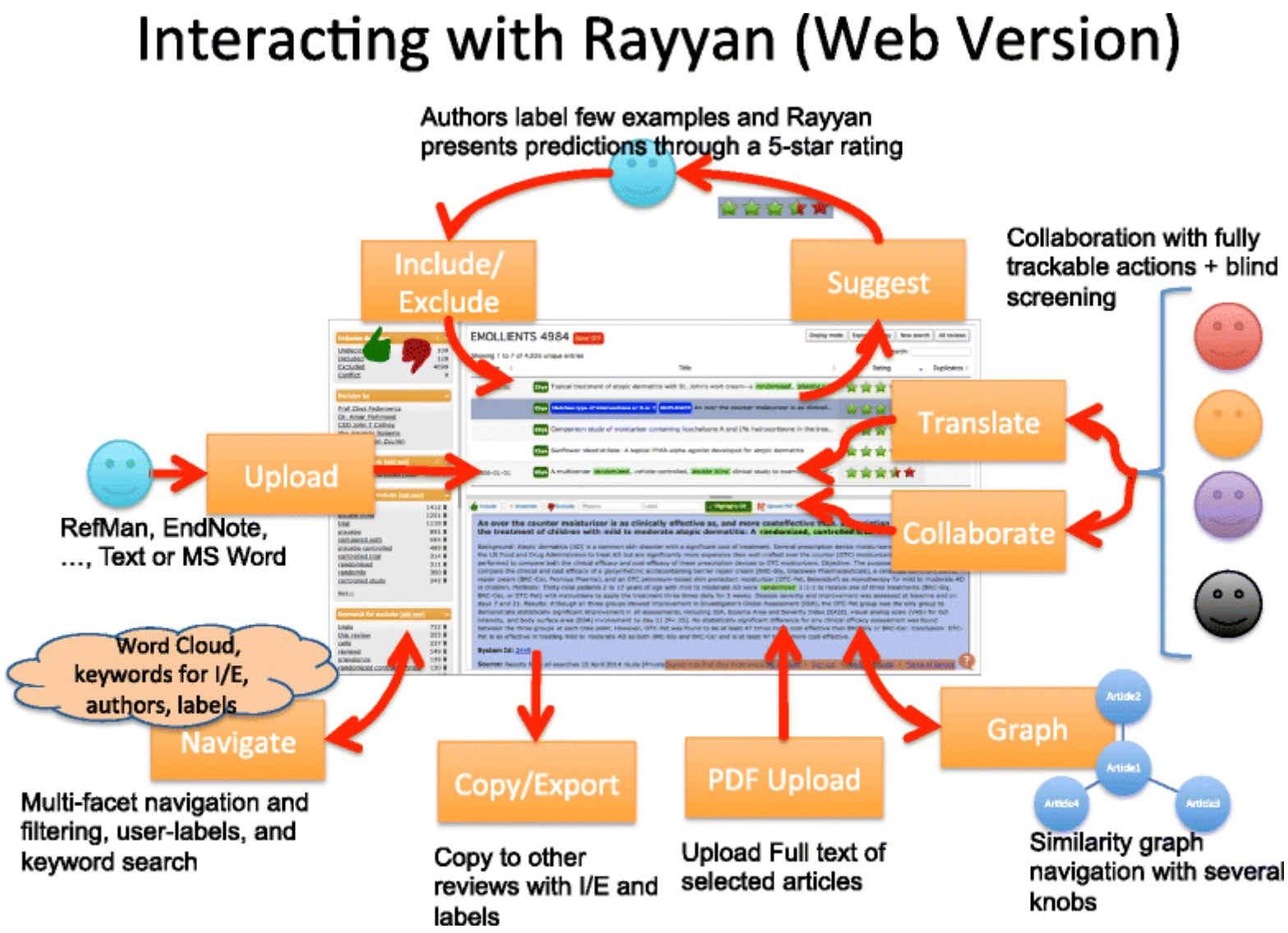
Clinical Information					Tests				
Past medical history	Seizure frequency in past month, Mean (SD)			Death	Vital signs	Targeted physical and neurological	Electrocardiogra	Laborat	Pregnancy
	Focal impaired awareness	Focal aware with motor features	Focal to biliateral tonic-clonic						
N/A	N/A								
Electroencephalogram that showed a pattern of slow (<3.0									

Treatment									
Type of CBD (Provided by STI Pharmaceuticals –	Total CBD dose/day	Baseline	Length of treatment	Dose escalation	Dose maintenance	Taper period	(Safety) Follow-up duration	Arm(s)	Control
Provided by GW Pharmaceuticals Solution contained 100 mg CBD	20 mg/kg/d	4 weeks	14 weeks	2 weeks	12 weeks	10 days	4 weeks	2	Placebo solution

Adverse events Case (Total)				Adverse events (CBD۵۰mg)				Adverse events (CBD۲۵mg)				Adverse events (CBD۲۰mg)				Adverse events (CBD۱۰mg)		
Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Mo
۵۷	۴۸		۹	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	۵۷	۴۸		۹	N/A	N/A	N
۴۶	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	۴۶	N/A	N/A	N/A	N/A	N/A	N
۷	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	۷	N/A	N/A	N/A	N/A	N/A	N
۱۹	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	۱۹	N/A	N/A	N/A	N/A	N/A	N
۹	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	۹	N/A	N/A	N/A	N/A	N/A	N
۱۲	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	۱۲	N/A	N/A	N/A	N/A	N/A	N

Data Extraction Tools - Covidence

Data Extraction Tools - Rayyan



Ouzzani *et al. Systematic Reviews* (2016) 5:210
DOI 10.1186/s13643-016-0384-4

Systematic Reviews

METHODOLOGY Open Access

Rayyan—a web and mobile app for systematic reviews

Mourad Ouzzani[1*], Hossam Hammady[1], Zbys Fedorowicz[2] and Ahmed Elmagarmid[1]

Abstract

Background: Synthesis of multiple randomized controlled trials (RCTs) in a systematic review can summarize the effects of individual outcomes and provide numerical answers about the effectiveness of interventions. Filtering of searches is time consuming, and no single method fulfills the principal requirements of speed with accuracy. Automation of systematic reviews is driven by a necessity to expedite the availability of current best evidence for policy and clinical decision-making.

We developed Rayyan (http://rayyan.qcri.org), a free web and mobile app, that helps expedite the initial screening of abstracts and titles using a process of semi-automation while incorporating a high level of usability. For the beta testing phase, we used two published Cochrane reviews in which included studies had been selected manually. Their searches, with 1030 records and 273 records, were uploaded to Rayyan. Different features of Rayyan were tested using these two reviews. We also conducted a survey of Rayyan's users and collected feedback through a built-in feature.

Results: Pilot testing of Rayyan focused on usability, accuracy against manual methods, and the added value of the prediction feature. The "taster" review (273 records) allowed a quick overview of Rayyan for early comments on usability. The second review (1030 records) required several iterations to identify the previously identified 11 trials. The "suggestions" and "hints," based on the "prediction model," appeared as testing progressed beyond five included studies. Post rollout user experiences and a reflexive response by the developers enabled real-time modifications and improvements. The survey respondents reported 40% average time savings when using Rayyan compared to others tools, with 34% of the respondents reporting more than 50% time savings. In addition, around 75% of the respondents mentioned that screening and labeling studies as well as collaborating on reviews to be the two most important features of Rayyan.

As of November 2016, Rayyan users exceed 2000 from over 60 countries conducting hundreds of reviews totaling more than 1.6M citations. Feedback from users, obtained mostly through the app web site and a recent survey, has

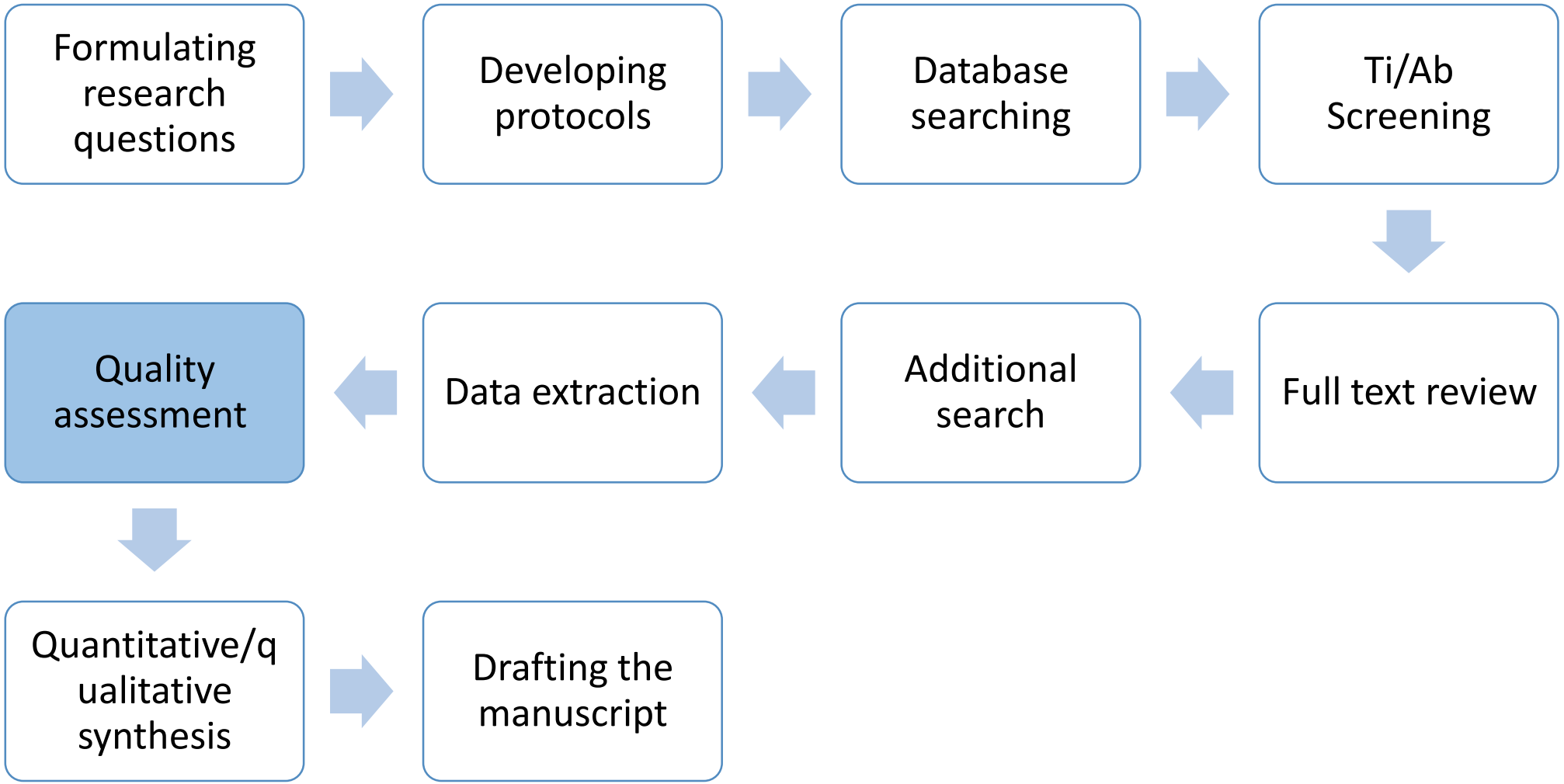
Data Extraction Tools - Rayyan

Sum Up- Any Questions?

- Data extraction items and process
- Data extraction tools
- Data transformation

- Highlight Key Data in PDFs
- Use clear and descriptive file names for easy identification.
- Design a structured spreadsheet with columns for key variables.
- Extract only one number per cell to maintain clarity and usability.

Summary Steps of Systematic Review



Quality Assessment

- **Definition**
- Bias refers to the systematic distortion of study results, leading to underestimation or overestimation of the true intervention effect.
- RoB arises from flaws in study design, conduct, or analysis (e.g., lack of blinding, selection bias).
- It is often impossible to determine the exact impact of methodological flaws on results.
- **Key Concepts in RoB:**
- RoB reflects the likelihood of distortion in results but does not confirm bias.
- Example: Lack of blinding may lead to overestimation in one study but underestimation in another
- **Assessment Tools:**
- Several checklists are available to evaluate study quality.

Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better?

Table 1 The basic characteristics of the included methodological quality (risk of bias) assessment tools

No.	Development Organization	Tool's name	Type of study
1	The Cochrane Collaboration	Cochrane RoB tool and RoB 2.0 tool	Randomized controlled trial Diagnostic accuracy study
2	The Physiotherapy Evidence Database (PEDro)	PEDro scale	Randomized controlled trial
3	The Effective Practice and Organisation of Care (EPOC) Group	EPOC RoB tool	Randomized controlled trial Clinical controlled trials Controlled before-and-after study Interrupted time series studies
4	The Critical Appraisal Skills Programme (CASP)	CASP checklist	Randomized controlled trial Cohort study Case-control study Cross-sectional study Diagnostic test study Clinical prediction rule Economic evaluation Qualitative study Systematic review
5	The National Institutes of Health (NIH)	NIH quality assessment tool	Controlled intervention study Cohort study Cross-sectional study Case-control study Before-after (Pre-post) study with no control group Case-series (Interventional) Systematic review and meta-analysis
6	The Joanna Briggs Institute (JBI)	JBI critical appraisal checklist	Randomized controlled trial Non-randomized experimental study Cohort study Case-control study Cross-sectional study Prevalence data Case reports Economic evaluation Qualitative study Text and expert opinion papers Systematic reviews and research syntheses
7	The Scottish Intercollegiate Guidelines Network (SIGN)	SIGN methodology checklist	Randomized controlled trial Cohort study Case-control study Diagnostic study Economic evaluation Systematic reviews and meta-analyses

Ma, LL., Wang, YY., Yang, ZH. et al. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better?. Military Med Res 7, 7 (2020). https://doi.org/10.1186/s40779-020-00238-8

8	The Stroke Therapy Academic Industry Roundtable (STAIR) Group	CAMARADES tool	Animal study
9	The SYstematic Review Center for Laboratory animal Experimentation (SYRCLE)	SYRCLE's RoB tool	Animal study
10	Sterne JAC et al.	ROBINS-I tool	Non-randomised interventional study
11	Slim K et al.	MINORS tool	Non-randomised interventional study
12	The Canada Institute of Health Economics (IHE)	IHE quality appraisal tool	Case-series (Interventional)
13	Wells GA et al.	Newcastle-Ottawa Scale (NOS)	Cohort study Case-control study
14	Downes MJ et al.	AXIS tool	Cross-sectional study
15	The Agency for Healthcare Research and Quality (AHRQ)	AHRQ methodology checklist	Cross-sectional/ Prevalence study
16	Crombie I	Crombie's items	Cross-sectional study
17	The Good Research for Comparative Effectiveness (GRACE) Initiative	GRACE checklist	Comparative effectiveness research
18	Whiting PF et al.	QUADAS tool and QUADAS-2 tool	Diagnostic accuracy study
19	The National Institute for Clinical Excellence (NICE)	NICE methodology checklist	Economic evaluation
20	The Cabinet Office	The Quality Framework: Cabinet Office checklist	Qualitative study (social research)
21	Hayden JA et al.	QIPS tool	Prediction study (predictor finding study)
22	Wolff RF et al.	PROBAST	Prediction study (prediction model study)
23	The (COnsensus-based Standards for the selection of health Measurement INstruments) initiative	COSMIN RoB checklist	Patient-reported outcome measure development Content validity Structural validity Internal consistency Cross-cultural validity/ measurement invariance Reliability Measurement error Criterion validity Hypotheses testing for construct validity Responsiveness
24	Shea BJ et al.	AMSTAR and AMSTAR 2	Systematic review
25	The Decision Support Unit (DSU)	DSU network meta-analysis (NMA) methodology checklist	Network meta-analysis
26	Whiting P et al.	ROBIS tool	Systematic review
27	Brouwers MC et al.	AGREE instrument and AGREE II instrument	Clinical practice guideline

AMSTAR A measurement tool to assess systematic reviews, *AHRQ* Agency for healthcare research and quality, *AXIS* Appraisal tool for cross-sectional studies, *CASP* Critical appraisal skills programme, *CAMARADES* The collaborative approach to meta-analysis and review of animal data from experimental studies, *COSMIN* Consensus-based standards for the selection of health measurement instruments, *DSU* Decision support unit, *EPOC* the effective practice and organisation of care group, *GRACE* The god research for comparative effectiveness initiative, *IHE* Canada institute of health economics, *JBI* Joanna Briggs Institute, *MINORS* Methodological index for non-randomized studies, *NOS* Newcastle-Ottawa scale, *NMA* network meta-analysis, *NIH* national institutes of health, *NICE* National institute for clinical excellence, *PEDro* physiotherapy evidence database, *PROBAST* The prediction model risk of bias assessment tool, *QUADAS* Quality assessment of diagnostic accuracy studies, *QIPS* Quality in prognosis studies, *RoB* Risk of bias, *ROBINS-I* Risk of bias in non-randomised studies - of interventions, *ROBIS* Risk of bias in systematic review, *SYRCLE* Systematic review center for laboratory animal experimentation, *STAIR* Stroke therapy academic industry roundtable, *SIGN* The Scottish intercollegiate guidelines network

Quality Assessment Process

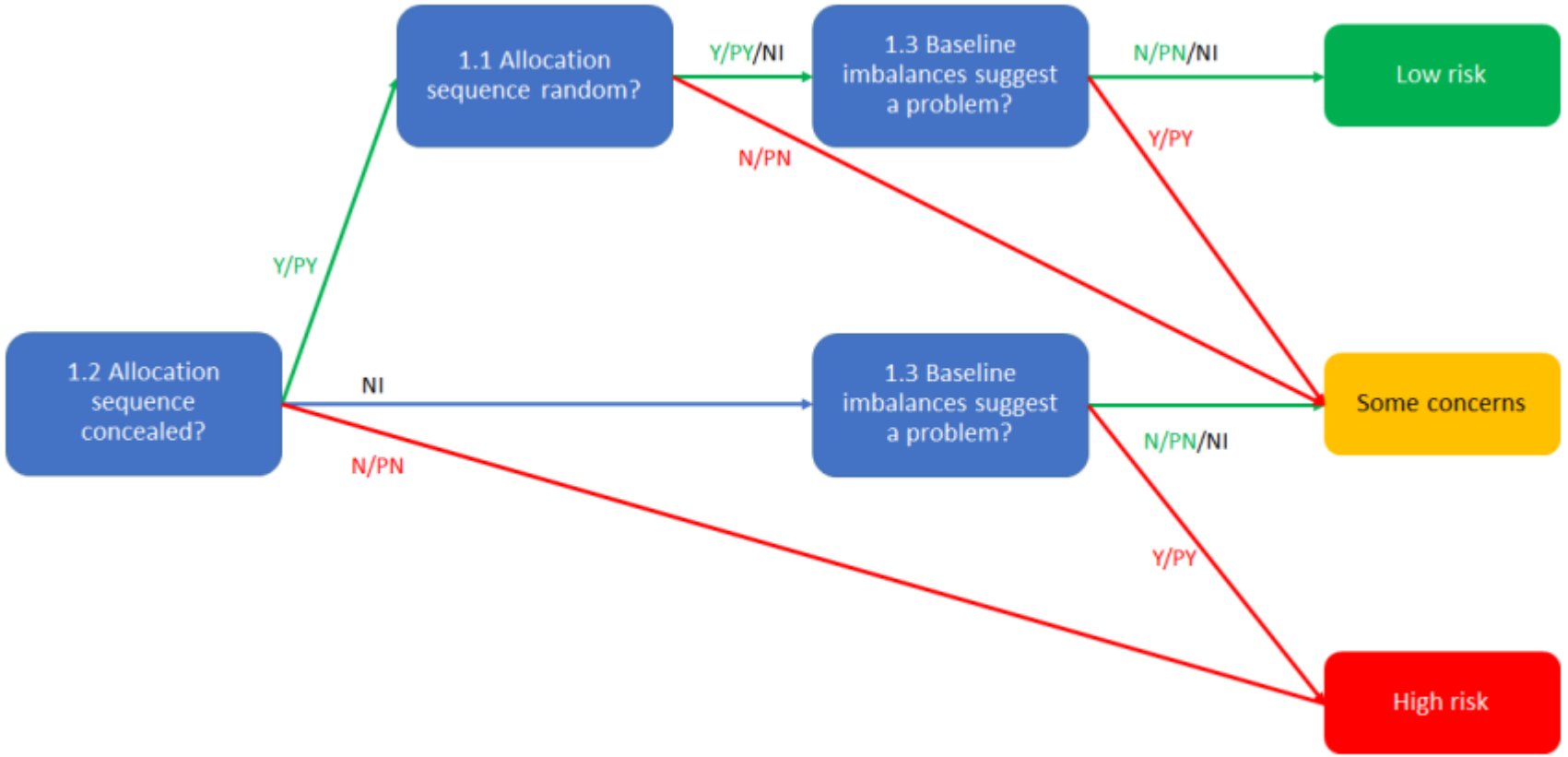
- Two researchers independently assess study quality using standardized forms.
- Reporting:
  - Report the percentage of agreement between researchers on quality assessments.
  - Present quality scores for each study in a summary table for transparency.

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Elaboration	Response options
1.1 Was the allocation sequence random?	Answer 'Yes' if a random component was used in the sequence generation process. Examples include computer-generated random numbers; reference to a random number table; coin tossing; shuffling cards or envelopes; throwing dice; or drawing lots. Minimization is generally implemented with a random element (at least when the scores are equal), so an allocation sequence that is generated using minimization should generally be considered to be random. Answer 'No' if no random element was used in generating the allocation sequence or the sequence is predictable. Examples include alternation; methods based on dates (of birth or admission); patient record numbers; allocation decisions made by clinicians or participants; allocation based on the availability of the intervention; or any other systematic or haphazard method. Answer 'No information' if the only information about randomization methods is a statement that the study is randomized. In some situations a judgement may be made to answer 'Probably no' or 'Probably yes'. For example, , in the context of a large trial run by an experienced clinical trials unit, absence of specific information about generation of the randomization sequence, in a paper published in a journal with rigorously enforced word count limits, is likely to result in a response of 'Probably yes' rather than 'No information'. Alternatively, if other (contemporary) trials by the same investigator team have clearly used non-random sequences, it might be reasonable to assume that the current study was done using similar methods.	Y/PY/PN/N/NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Answer 'Yes' if the trial used any form of remote or centrally administered method to allocate interventions to participants, where the process of allocation is controlled by an external unit or organization, independent of the enrolment personnel (e.g. independent central pharmacy, telephone or internet-based randomization service providers). Answer 'Yes' if envelopes or drug containers were used appropriately. Envelopes should be opaque, sequentially numbered, sealed with a tamper-proof seal and opened only after the envelope has been irreversibly assigned to the participant. Drug containers should be sequentially numbered and of identical appearance, and dispensed or administered only after they have been irreversibly assigned to the participant. This level of detail is rarely provided in reports, and a judgement may be required to justify an answer of 'Probably yes' or 'Probably no'. Answer 'No' if there is reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation.	Y/PY/PN/N/NI

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)



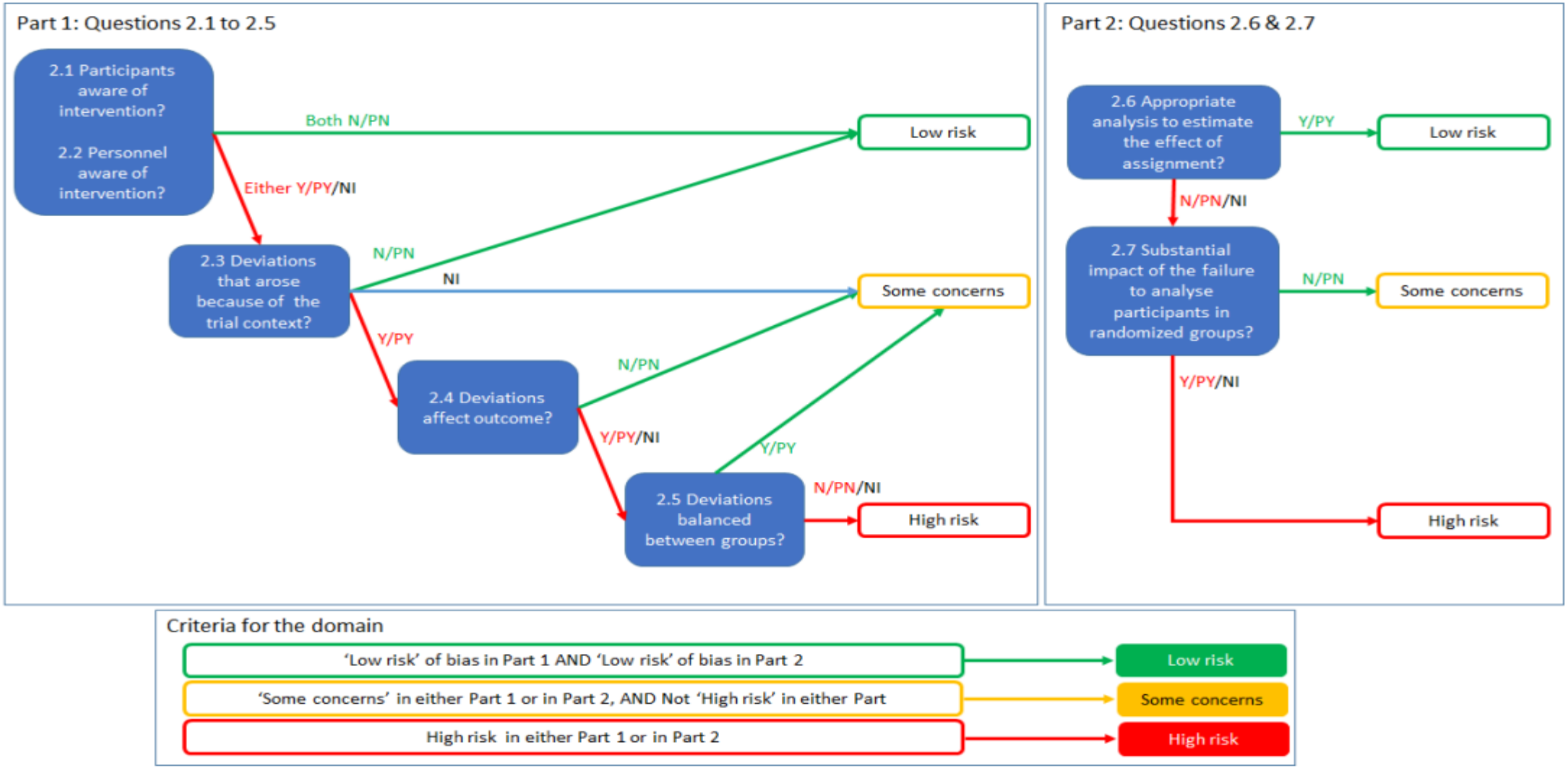
Algorithm for suggested judgement of risk of bias arising from the randomization process

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Elaboration	Response options
2.1. Were participants aware of their assigned intervention during the trial?	If participants are aware of their assigned intervention it is more likely that health-related behaviours will differ between the intervention groups. Blinding participants, most commonly through use of a placebo or sham intervention, may prevent such differences. If participants experienced side effects or toxicities that they knew to be specific to one of the interventions, answer this question 'Yes' or 'Probably yes'.	Y/PY/PN/N/NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	If carers or people delivering the interventions are aware of the assigned intervention then its implementation, or administration of non-protocol interventions, may differ between the intervention groups. Blinding may prevent such differences. If participants experienced side effects or toxicities that carers or people delivering the interventions knew to be specific to one of the interventions, answer question 'Yes' or 'Probably yes'. If randomized allocation was not concealed, then it is likely that carers and people delivering the interventions were aware of participants' assigned intervention during the trial.	Y/PY/PN/N/NI

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)



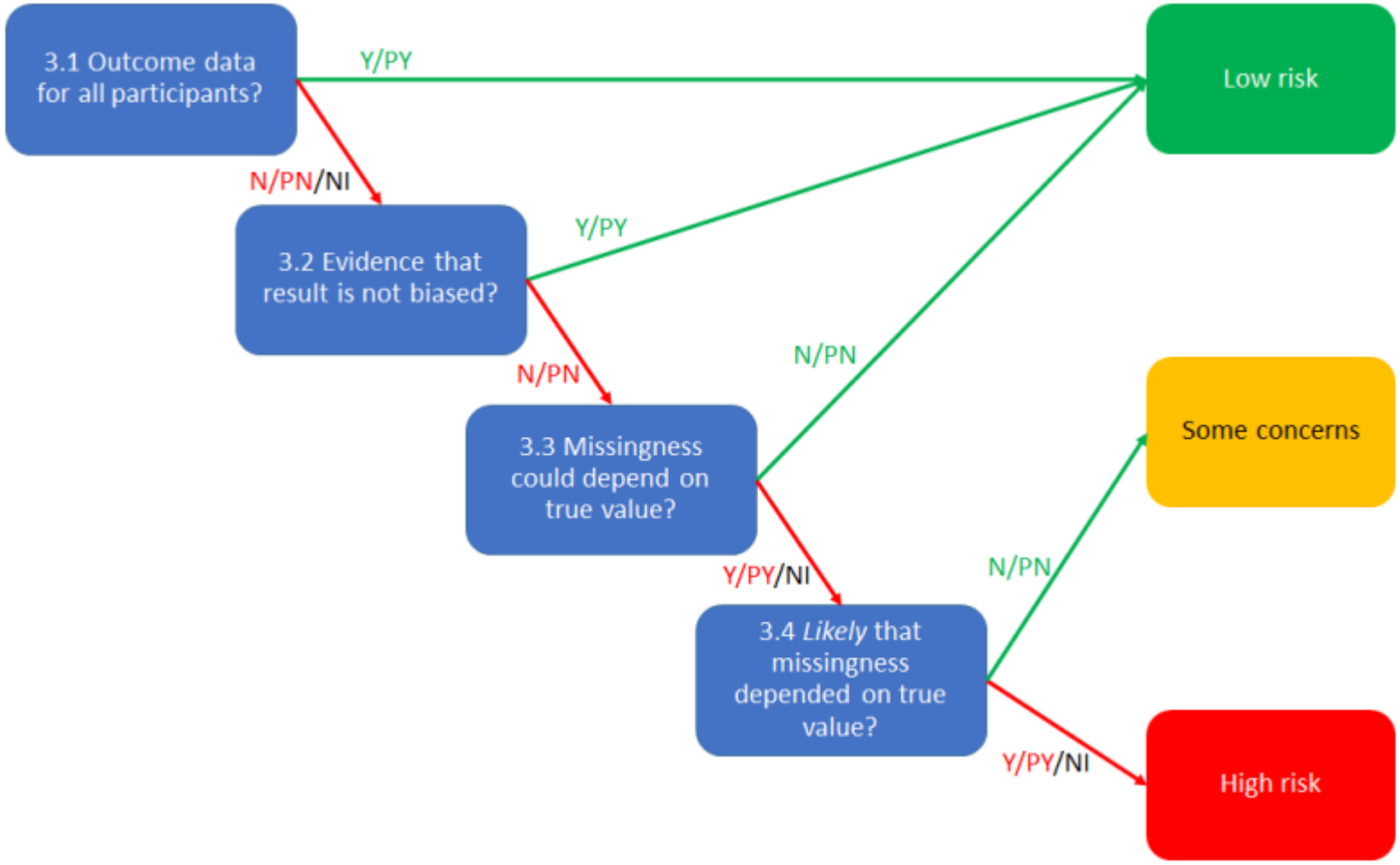
Algorithm for suggested judgement of risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Elaboration	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	The appropriate study population for an analysis of the intention to treat effect is all randomized participants. "Nearly all" should be interpreted as that the number of participants with missing outcome data is sufficiently small that their outcomes, whatever they were, could have made no important difference to the estimated effect of intervention. For continuous outcomes, availability of data from 95% of the participants will often be sufficient. For dichotomous outcomes, the proportion required is directly linked to the risk of the event. If the observed number of events is much greater than the number of participants with missing outcome data, the bias would necessarily be small. Only answer 'No information' if the trial report provides no information about the extent of missing outcome data. This situation will usually lead to a judgement that there is a high risk of bias due to missing outcome data. Note that imputed data should be regarded as missing data, and not considered as 'outcome data' in the context of this question.	Y/PY/PN/N/NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Evidence that the result was not biased by missing outcome data may come from: (1) analysis methods that correct for bias; or (2) sensitivity analyses showing that results are little changed under a range of plausible assumptions about the relationship between missingness in the outcome and its true value. However, imputing the outcome variable, either through methods such as 'last-observation-carried-forward' or via multiple imputation based only on intervention group, should not be assumed to correct for bias due to missing outcome data.	NA/Y/PY/PN/N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	If loss to follow up, or withdrawal from the study, could be related to participants' health status, then it is possible that missingness in the outcome was influenced by its true value. However, if all missing outcome data occurred for documented reasons that are unrelated to the outcome then the risk of bias due to missing outcome data will be low (for example, failure of a measuring device or interruptions to routine data collection). In time-to-event analyses, participants censored during trial follow-up, for example because they withdrew from the study, should be regarded as having missing outcome data, even though some of their follow up is included in the analysis. Note that such participants may be shown as included in analyses in CONSORT flow diagrams.	NA/Y/PY/PN/N/NI

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)



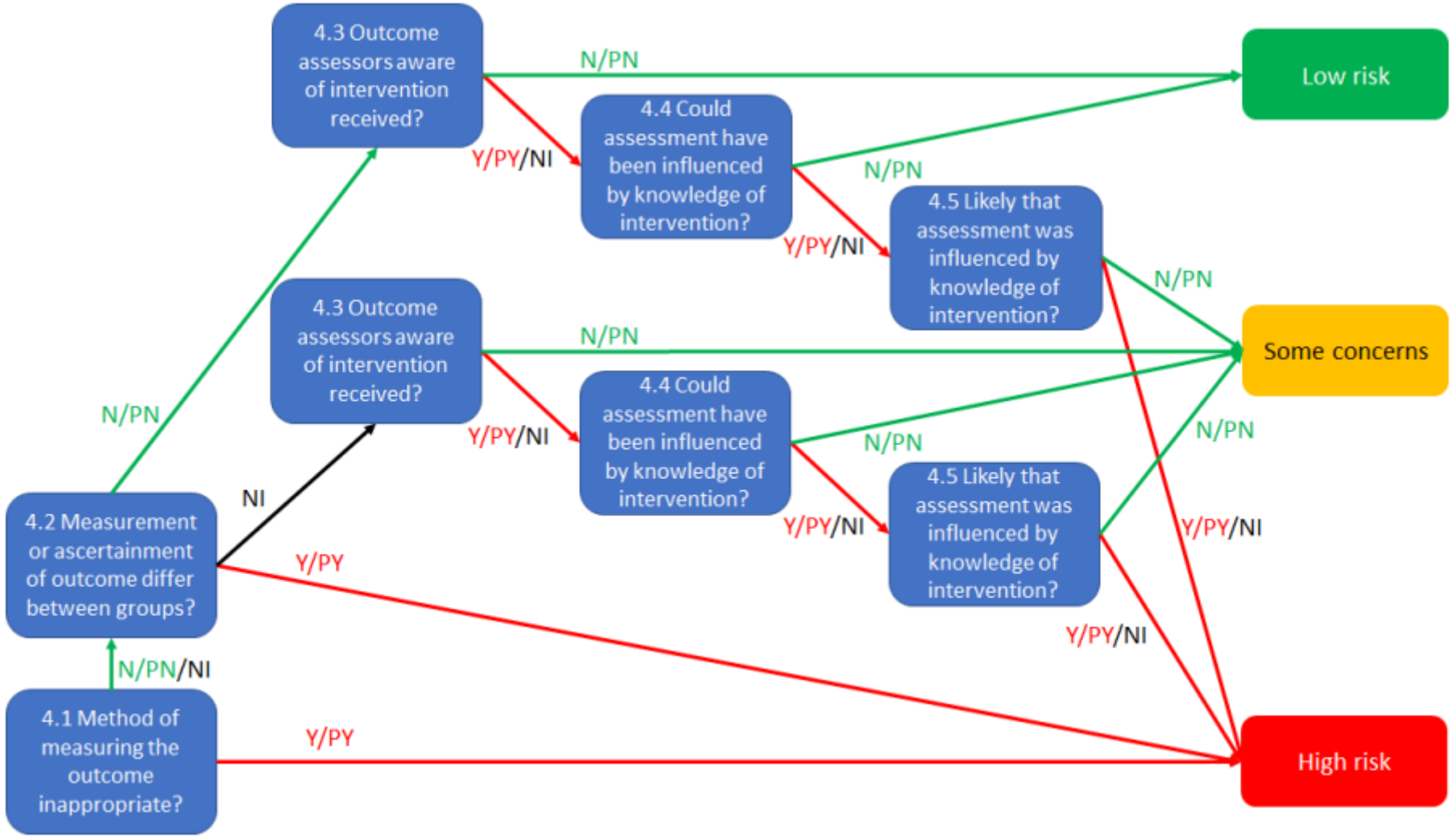
Algorithm for suggested judgement of risk of bias due to missing outcome data

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Elaboration	Response options
4.1 Was the method of measuring the outcome inappropriate?	This question aims to identify methods of outcome measurement (data collection) that are unsuitable for the outcome they are intended to evaluate. The question *does not* aim to assess whether the choice of outcome being evaluated was sensible (e.g. because it is a surrogate or proxy for the main outcome of interest). In most circumstances, for pre-specified outcomes, the answer to this question will be 'No' or 'Probably no'. Answer 'Yes' or 'Probably yes' if the method of measuring the outcome is inappropriate, for example because: (1) it is unlikely to be sensitive to plausible intervention effects (e.g. important ranges of outcome values fall outside levels that are detectable using the measurement method); or (2) the measurement instrument has been demonstrated to have poor validity.	Y/PY/PN/N/NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement (data collection) involve the same measurement methods and thresholds, used at comparable time points. Differences between intervention groups may arise because of 'diagnostic detection bias' in the context of passive collection of outcome data, or if an intervention involves additional visits to a healthcare provider, leading to additional opportunities for outcome events to be identified.	Y/PY/PN/N/NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Answer 'No' if outcome assessors were blinded to intervention status. For participant-reported outcomes, the outcome assessor is the study participant.	NA/Y/PY/PN/N/NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Knowledge of the assigned intervention could influence participant-reported outcomes (such as level of pain), observer-reported outcomes involving some judgement, and intervention provider decision outcomes. They are unlikely to influence observer-reported outcomes that do not involve judgement, for example all-cause mortality.	NA/Y/PY/PN/N/NI

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)



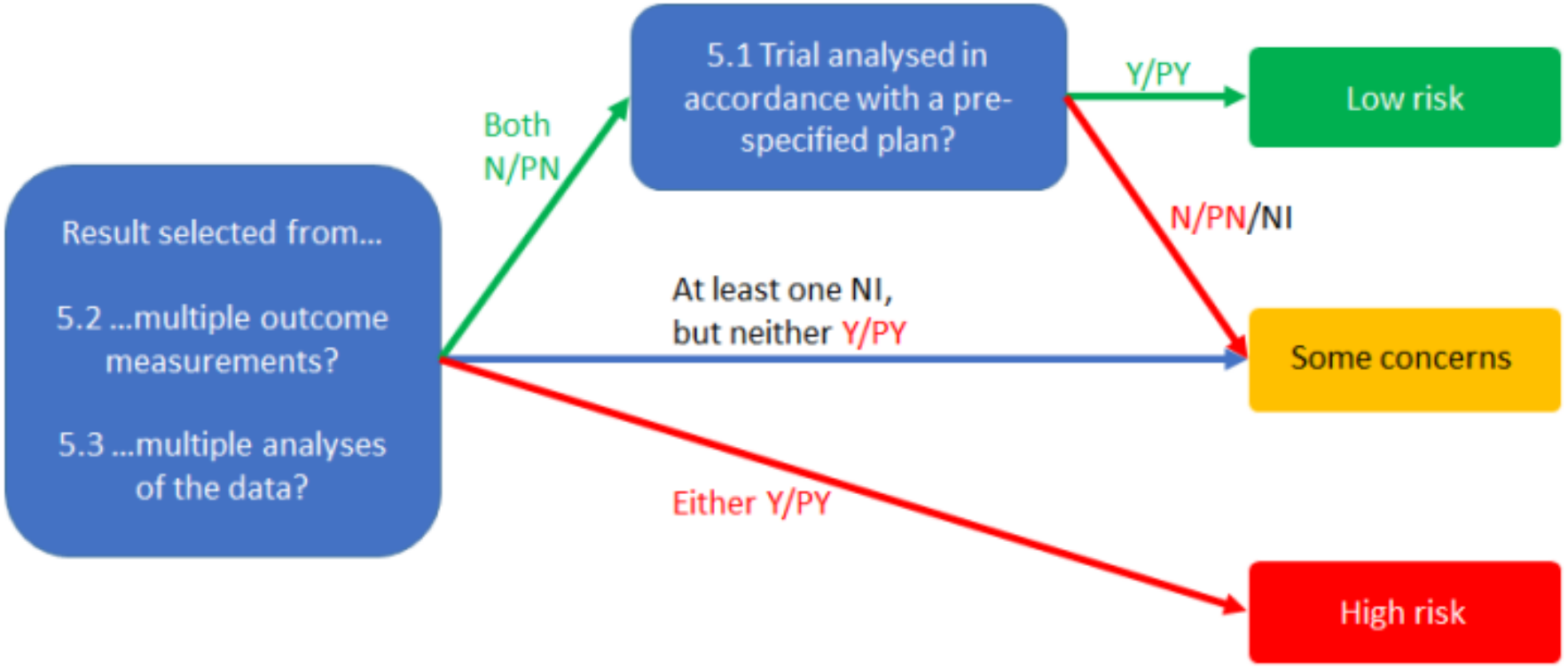
Algorithm for suggested judgement of risk of bias in measurement of the outcome

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Elaboration	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	If the researchers' pre-specified intentions are available in sufficient detail, then planned outcome measurements and analyses can be compared with those presented in the published report(s). To avoid the possibility of selection of the reported result, finalization of the analysis intentions must precede availability of unblinded outcome data to the trial investigators. Changes to analysis plans that were made before unblinded outcome data were available, or that were clearly unrelated to the results (e.g. due to a broken machine making data collection impossible) do not raise concerns about bias in selection of the reported result.	Y/PY/PN/N/NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	A particular outcome domain (i.e. a true state or endpoint of interest) may be **measured** in multiple ways. For example, the domain pain may be measured using multiple scales (e.g. a visual analogue scale and the McGill Pain Questionnaire), each at multiple time points (e.g. 3, 6 and 12 weeks post-treatment). If multiple measurements were made, but only one or a subset is reported on the basis of the results (e.g. statistical significance), there is a high risk of bias in the fully reported result. Attention should be restricted to outcome measurements that are eligible for consideration by the RoB 2 tool user. For example, if only a result using a specific measurement scale is eligible for inclusion in a meta-analysis (e.g. Hamilton Depression Rating Scale), and this is reported by the trial, then there would not be an issue of selection even if this result was reported (on the basis of the results) in preference to the result from a different measurement scale (e.g. Beck Depression Inventory). Answer 'Yes' or 'Probably yes' if: There is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that a domain was measured in multiple eligible ways, but data for only one or a subset of measures is fully reported (without justification), and the fully reported result is likely to have been selected on the basis of the results. Selection on the basis of the results can arise from a desire for findings to be newsworthy, sufficiently noteworthy to merit publication, or to confirm a prior hypothesis. For example, trialists who have a preconception, or vested interest in showing, that an	Y/PY/PN/N/NI

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

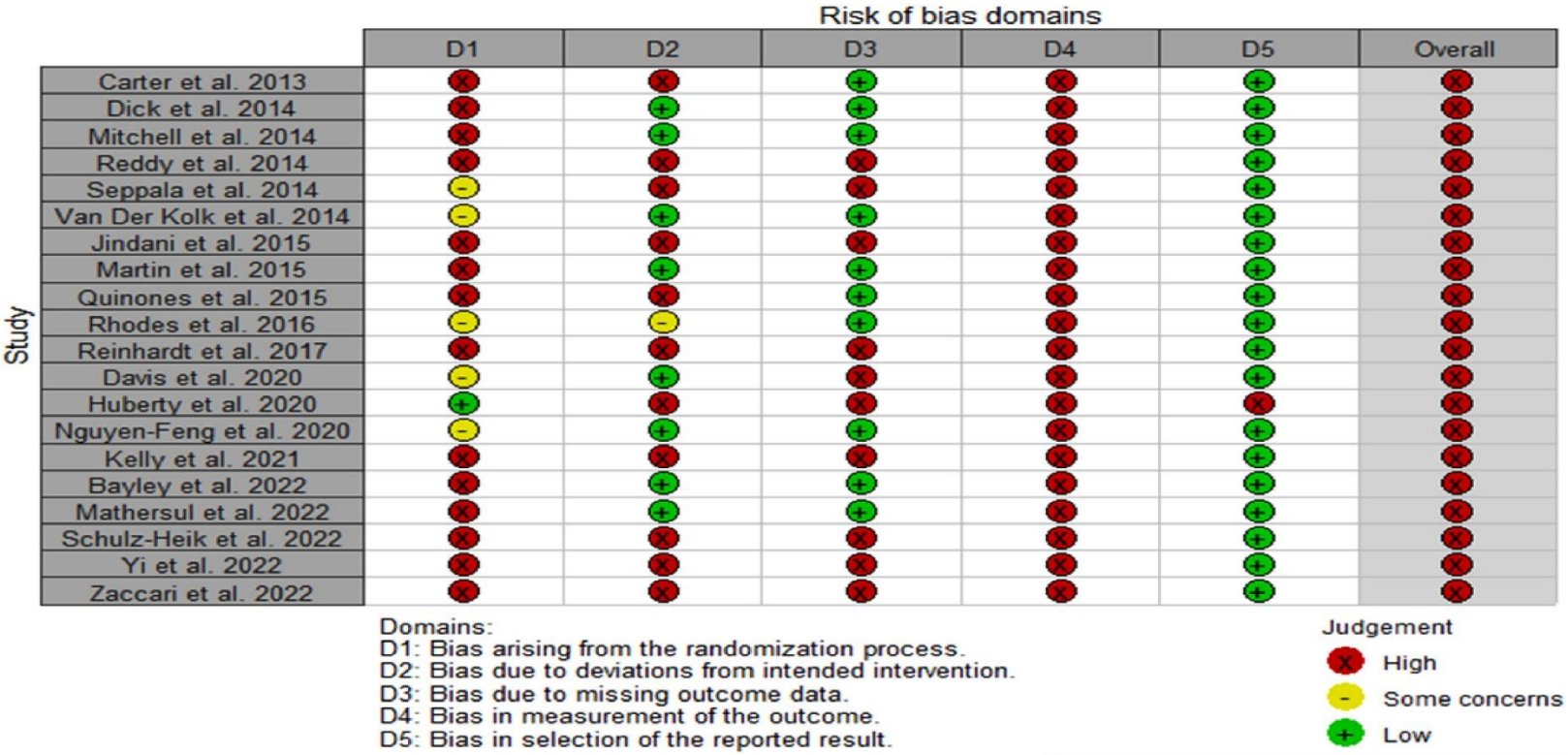


Algorithm for suggested judgement of risk of bias in selection of the reported result

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Overall risk-of-bias judgement	**Criteria**
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to raise **some concerns** in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. Or The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

Summary plot and traffic light plot



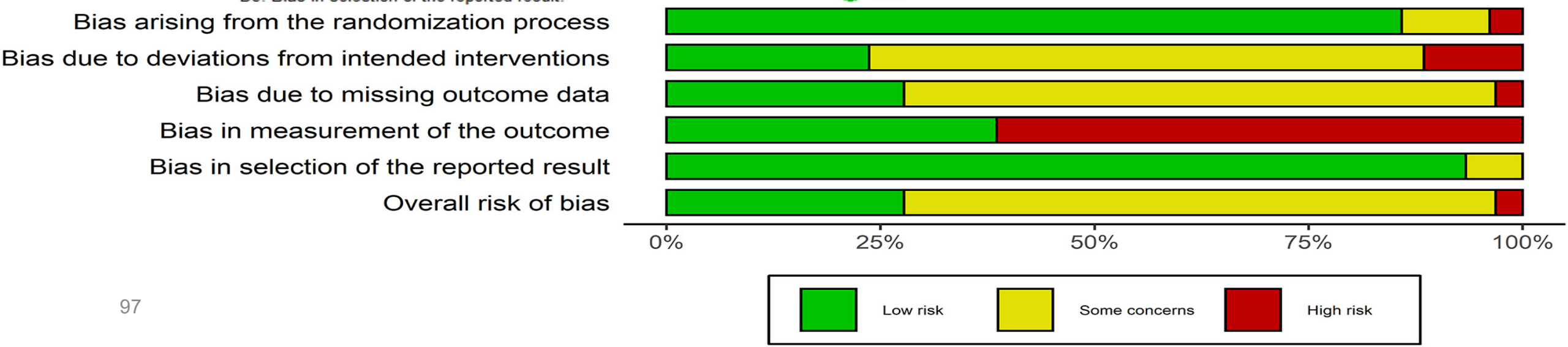


Table of Quality Assessment Example

eTable 2. Quality assessment of the included studies.

Study ID	D1	D2	D3	D4	D5	Overall bias
Devinsky et al. 2017 (1)	Low	Low	Low	Some concerns	Low	Some concerns
Devinsky et al. 17, 2018 (2)	Low	Low	Low	High	High	High
Devinsky et al. 14, 2018 (3)	Low	Low	Low	Some concerns	High	High
Thiele et al. 2018 (4)	Low	Low	Low	Low	Low	Low
Ben-Menachem et al. 2020 (5)	Low	Low	Low	Some concerns	Low	Some concerns
Miller et al. 2020 (6)	Low	Low	Low	Low	Low	Low
VanLandingham et al. 2020 (7)	Low	Low	Low	Some concerns	Low	Some concerns
Thiele et al. 2020 (8)	Low	Low	Low	Low	Low	Low
O'Brien et al. 2022 (9)	Low	Low	Low	High	Low	High

D1: Bias arising from the randomization process

D2: Bias due to deviations from intended interventions

D3: Bias due to missing outcome data

D4: Bias in measurement of the outcome

D5: Bias in selection of the reported results

RoB2 overall risk of bias judgment

Low risk of bias → The study is judged to be at low risk of bias for all domains for this result.

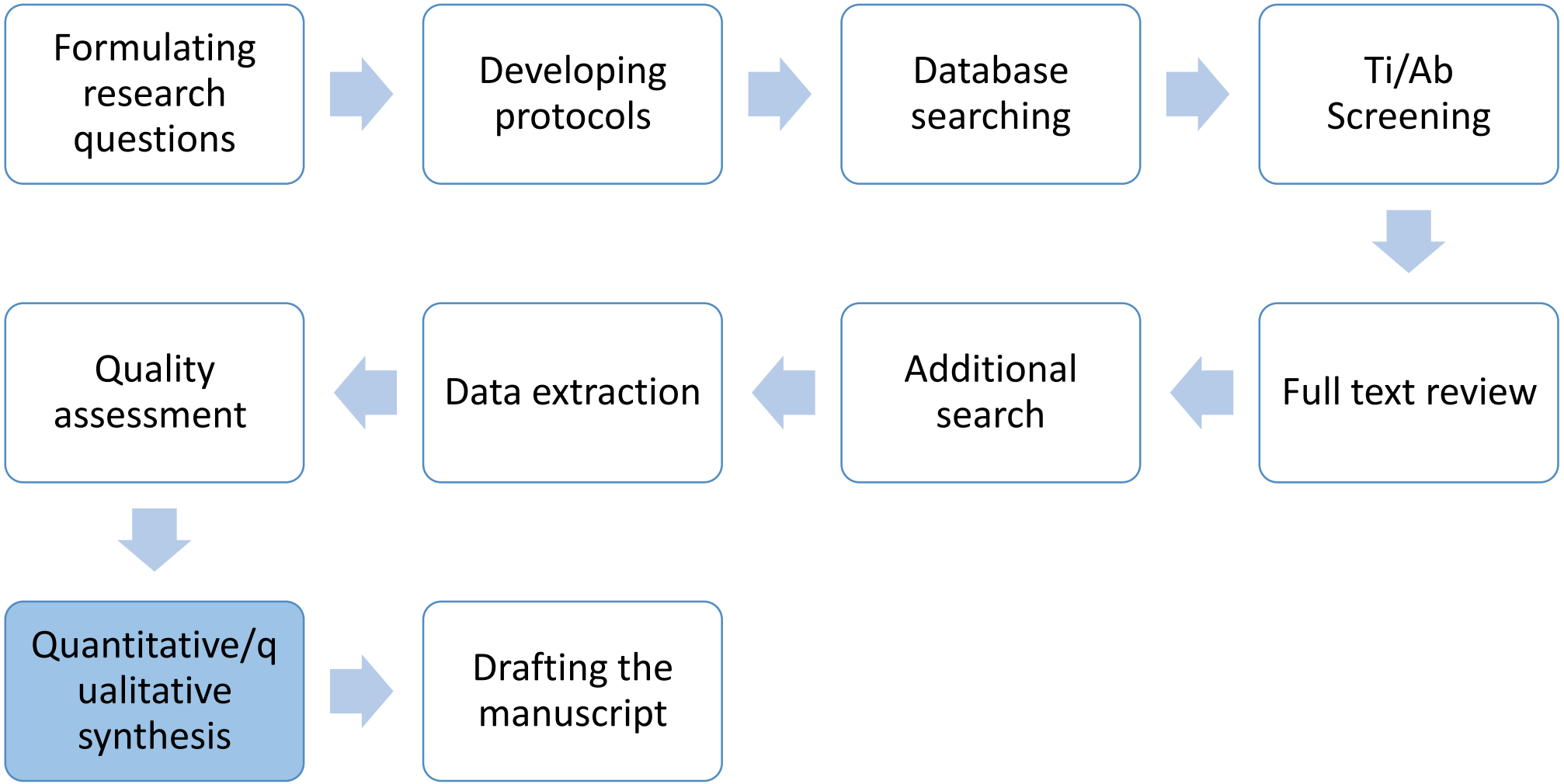
Some concerns → The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

High risk of bias → The study is judged to be at high risk of bias in at least one domain, or to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Sum Up- Any Questions?

- Quality assessment process
- Quality assessment tools

Summary Steps of Systematic Review



What is Meta-Analysis?

- Statistical method combining results from two or more separate studies.
- Provides an overall estimate of intervention effects with improved precision.
- Useful for resolving controversies, addressing broader questions, and exploring consistency across populations.

Benefits and Risks of Meta-Analysis

- Advantages:
  - Increases precision by pooling data from multiple studies.
  - Answers questions not posed by individual studies.
  - Resolves conflicting evidence and explores new hypotheses.
- Risks:
  - Can mislead if study designs, biases, heterogeneity, and reporting biases are not carefully addressed.

Meta-Analysis Process

- Stage 1:
  - Calculate a summary statistic for each study (e.g., risk ratio, mean difference).
- Stage 2: Combine these using a weighted average:
  - Studies with more data or less variance receive greater weight.
  - Fixed-effect model: Assumes one true intervention effect across studies.
  - Random-effects model: Allows for variation in intervention effects between studies.

Meta-Analysis Process

۱. استخراج یک شاخص مشترک از تمام مطالعات اولیه

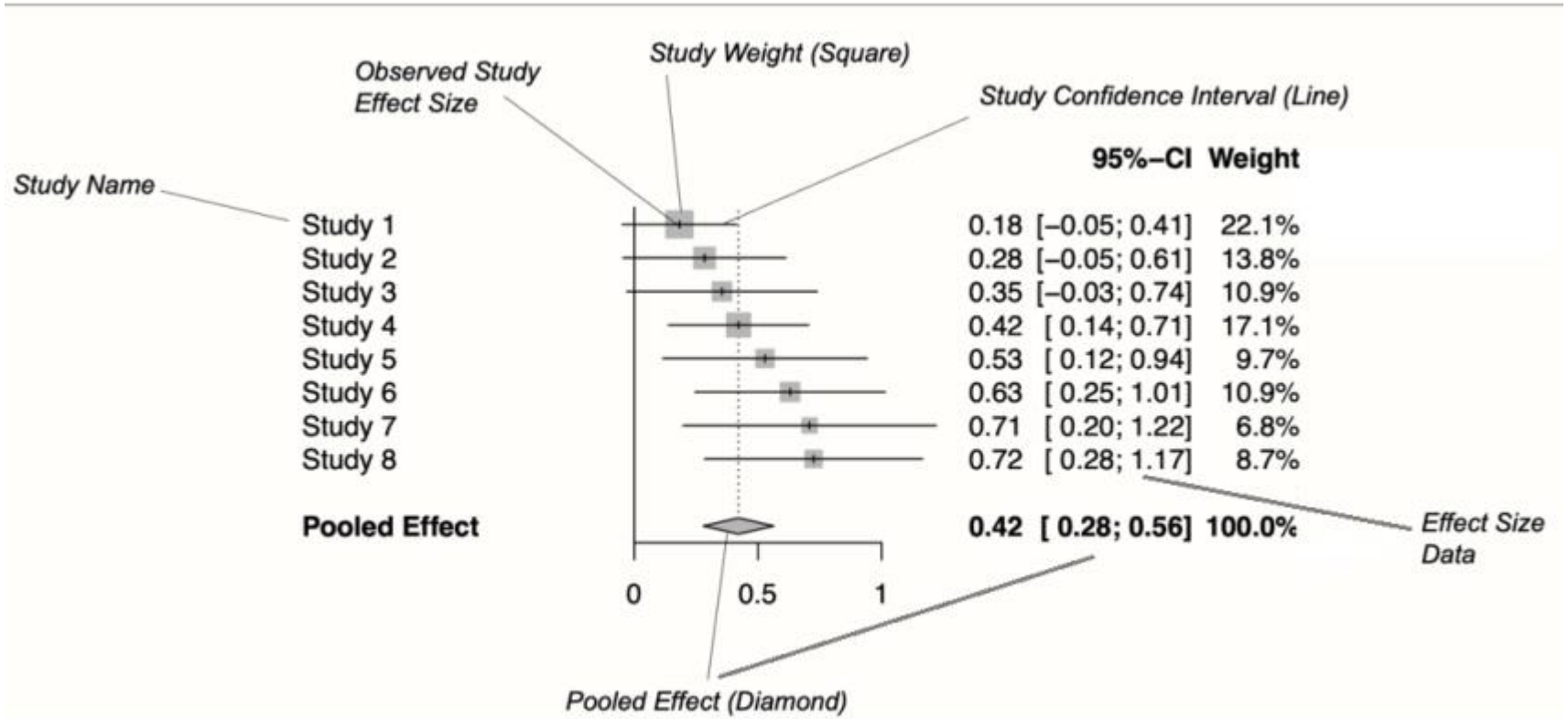
۲. ترکیب شاخص استخراج شده بر اساس نتایج مطالعات اولیه و محاسبه میانگین وزن داده شده.

۳. بررسی میزان عدم تجانس (هتروژنیتی) در نتایج مطالعات اولیه.

۴. اصلاح روشهای بکار گرفته شده بر اساس میزان عدم تجانس نتایج مطالعات اولیه و بررسی علل احتمالی ایجاد کننده آن از طریق روشهای آماری

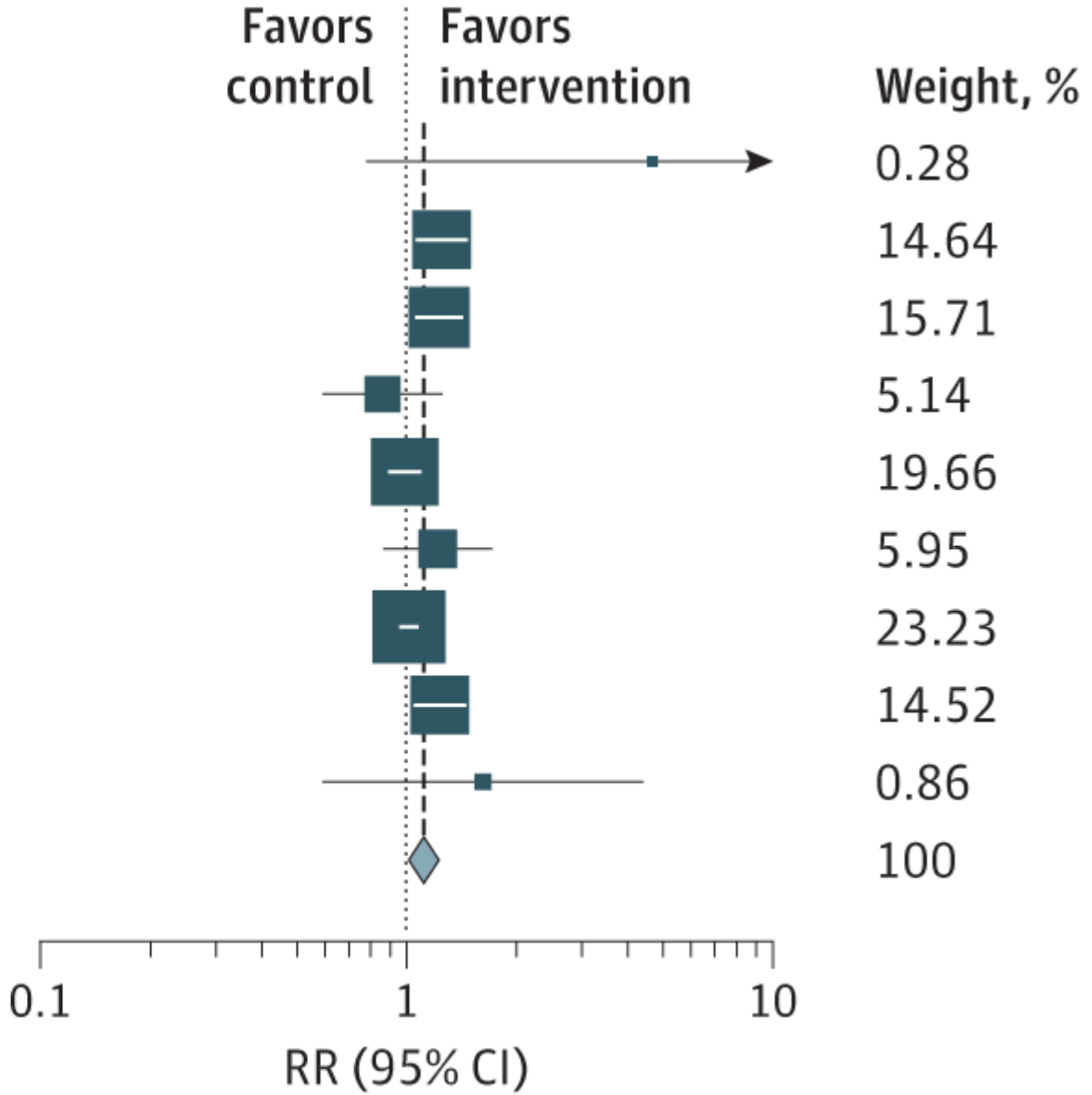
۵. ارایه نتایج بصورت روشن با استفاده صحیح از شاخص ها و نمودارهای مربوطه

Forest Plot

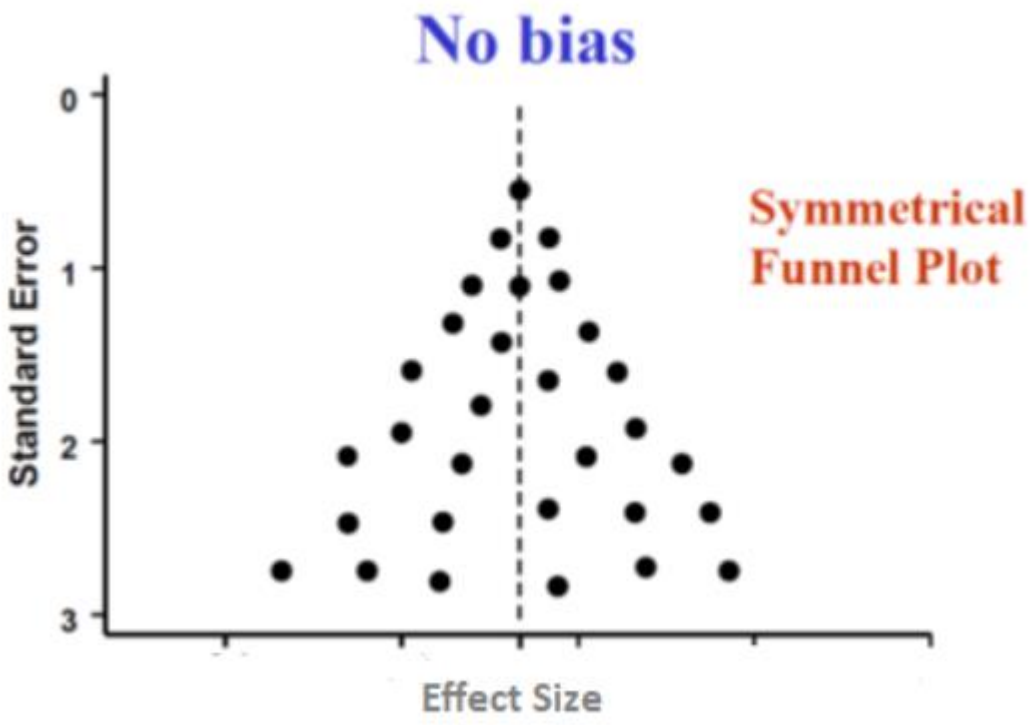

Observed Study Effect Size
Study Weight (Square)
Study Confidence Interval (Line)
Study Name
95%–CI Weight
Study 1 0.18 [–0.05; 0.41] 22.1%
Study 2 0.28 [–0.05; 0.61] 13.8%
Study 3 0.35 [–0.03; 0.74] 10.9%
Study 4 0.42 [0.14; 0.71] 17.1%
Study 5 0.53 [0.12; 0.94] 9.7%
Study 6 0.63 [0.25; 1.01] 10.9%
Study 7 0.71 [0.20; 1.22] 6.8%
Study 8 0.72 [0.28; 1.17] 8.7%
Pooled Effect 0.42 [0.28; 0.56] 100.0%
0
0.5
1
Effect Size Data
Pooled Effect (Diamond)

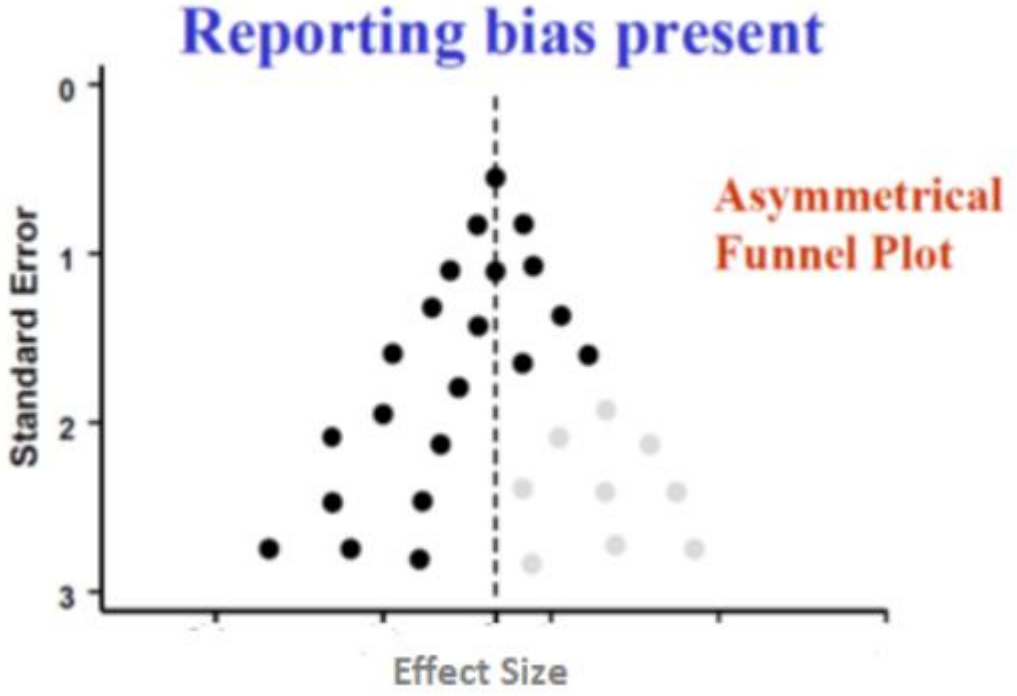
Forest Plot

Study	RR (95% CI)	Weight, %
Ben-Menachem et al,[74] 2020	4.71 (0.78-28.51)	0.28
Devinsky et al,[75] 2017	1.25 (1.06-1.48)	14.64
Devinsky et al,[76] 2018	1.23 (1.06-1.43)	15.71
Devinsky et al,[77] 2018	0.86 (0.59-1.26)	5.14
Miller et al,[78] 2020	0.99 (0.90-1.10)	19.66
O'Brien et al,[79] 2022	1.22 (0.87-1.72)	5.95
Thiele et al,[80] 2021	1.02 (0.96-1.08)	23.23
Thiele et al,[81] 2018	1.24 (1.05-1.46)	14.52
VanLandingham et al,[82] 2020	1.63 (0.59-4.45)	0.86
Overall: DL (I^2 = 58.9%; P = .01)	1.12 (1.02-1.23)	100



Funnel Plot

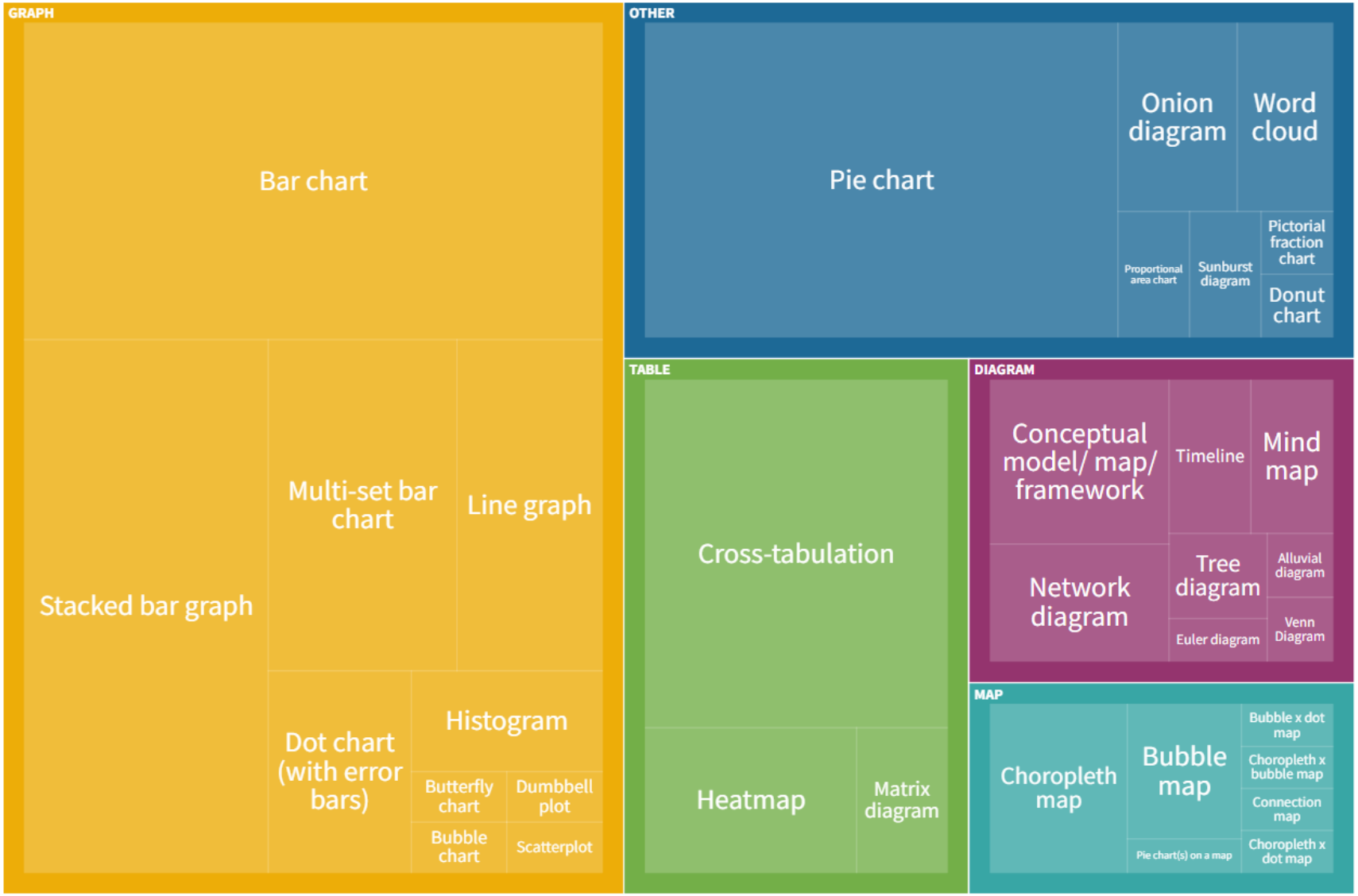

No bias
Standard Error
0
1
2
3
Effect Size
Symmetrical
Funnel Plot


Reporting bias present
Standard Error
0
1
2
3
Effect Size
Asymmetrical
Funnel Plot

Narrative Synthesis Overview

- Definition:
  - A systematic approach using words and text to summarize and explain findings across multiple studies.
- Key Characteristic:
  - Analyzes relationships within and between studies.
- Not be confused with a narrative review, as it is systematic and based on a predefined review question and protocol.
- Used when meta-analysis is not possible or practical.

Data visualization identified in scoping reviews



Tabular Example of Data Presentation

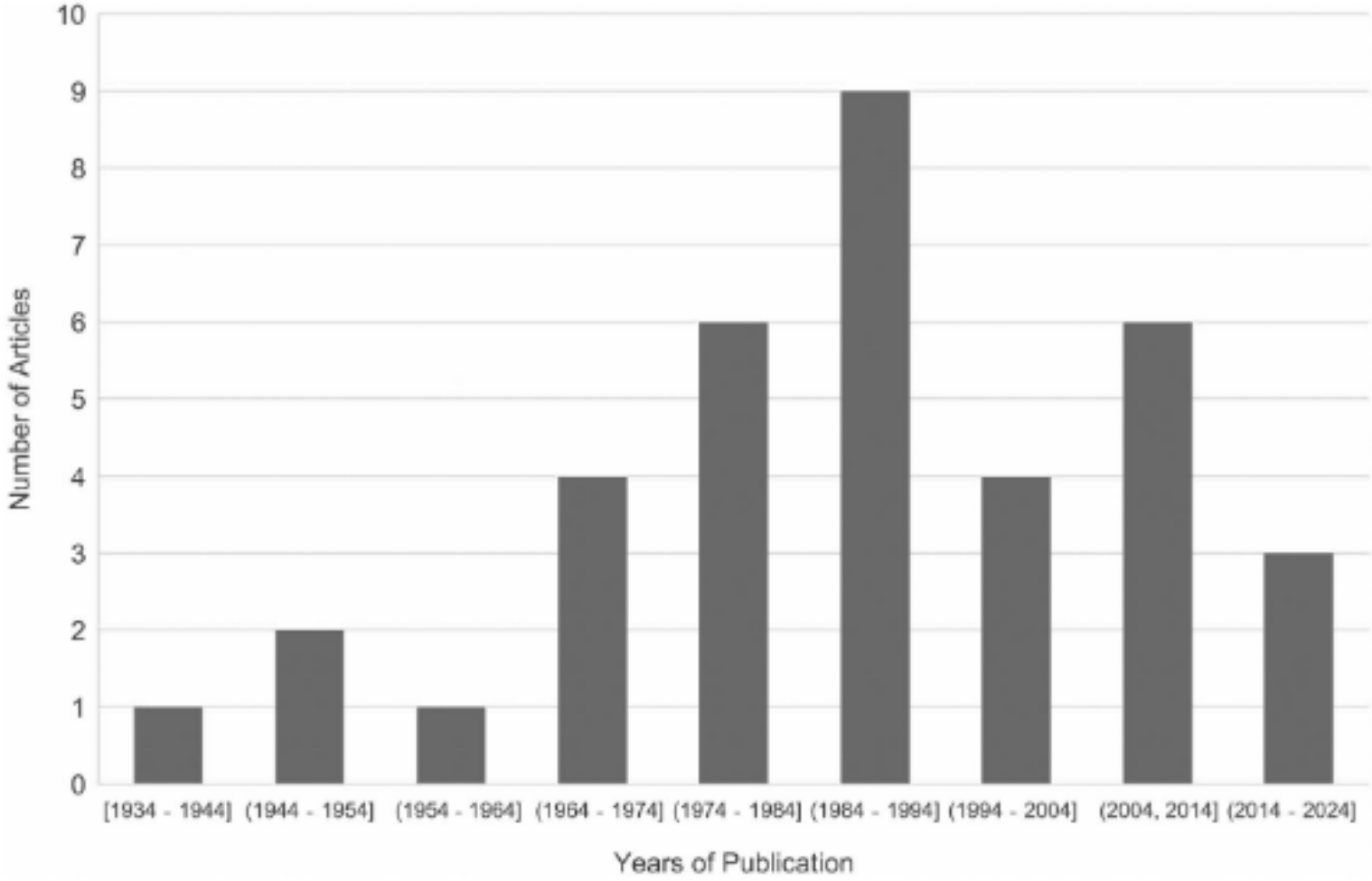
Category	Details
Numbers of Publications	- Total number, annual breakdown
Types of Studies	- RCTs, Cohort studies, Case-control studies
Populations Identified	- Children, adults, caregivers, professionals
Key Findings	- Summary of findings across studies

Table 2. Summary of characteristics of included studies.

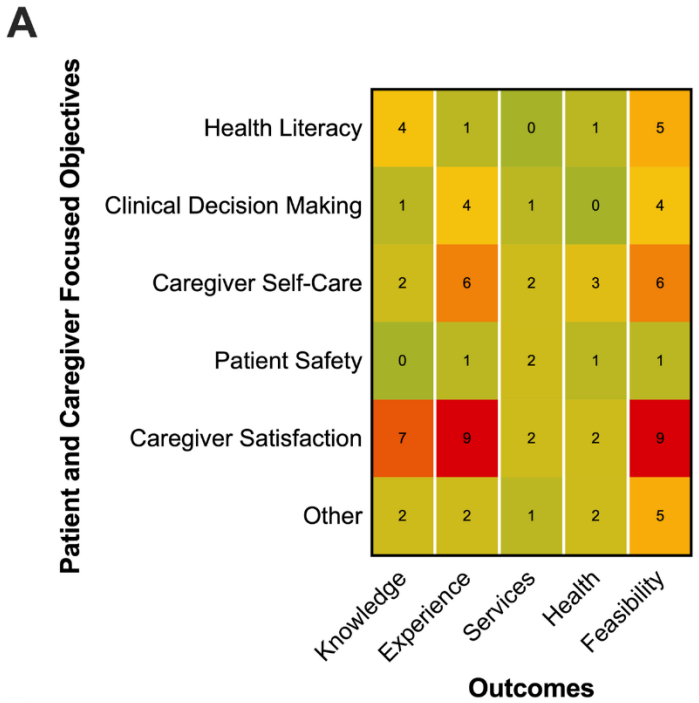
Characteristic	N	% of Studies
Study location		
United States	20	50%
Canada	3	7.5%
Holland	3	7.5%
Japan	2	5%
Belgium	1	2.5%
China	1	2.5%
England	1	2.5%
Estonia	1	2.5%
France	1	2.5%
Greece	1	2.5%
Poland	1	2.5%
Spain	1	2.5%
Nature of investigation		
Cross-sectional	29	72.5%
Prospective	10	25%
Longitudinal	1	2.5%
Capacities explored		
Motor	25	62.5%
Tactile	15	37.5%
Cognitive	5	12.5%
Exploring multiple capacities	6	15%
Braille reading measures explored		
Speed	33	82.5%
Accuracy	14	35%
Comprehension	3	7.5%
Capacity[a]	3	7.5%
Exploring multiple measures	13	32.5%
Age groups represented in sample		
Indeterminate[b]	8	20%
Children (< 10)	11	27.5%
Youth (10 – 18)	20	50%
Adults (19 – 59)	16	40%
Older adults (60+)	13	32.5%

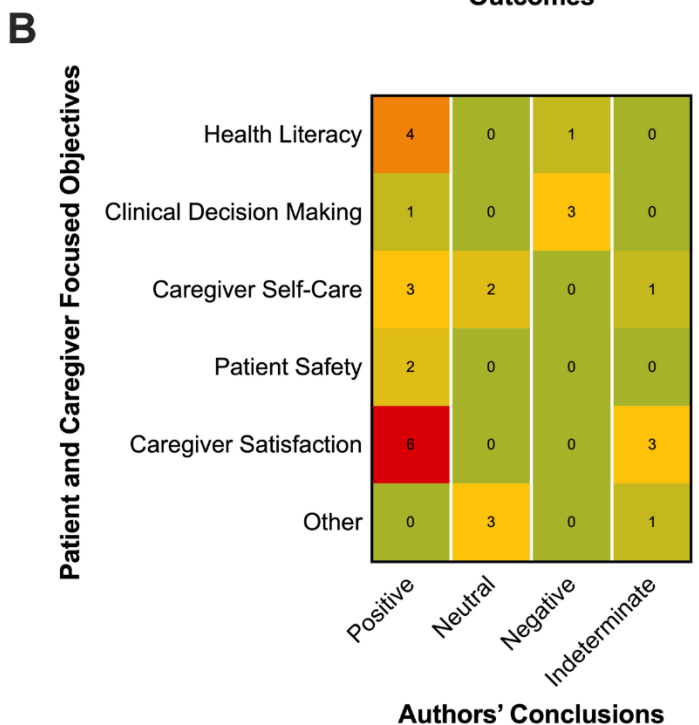
[a]These studies measured braille reading performance on a binary "can vs cannot read" basis, or described reading performance as "poor/fair/very good" without any further explanation as to the meaning of these descriptions.
[b]Insufficient information was provided in these studies to determine the age range of participants.

Bar chart


10
9
8
7
6
5
4
3
2
1
0
Number of Articles
[1934 - 1944]
(1944 - 1954]
(1954 - 1964]
(1964 - 1974]
(1974 - 1984]
(1984 - 1994]
(1994 - 2004]
(2004, 2014]
(2014 - 2024]
Years of Publication

Heat map



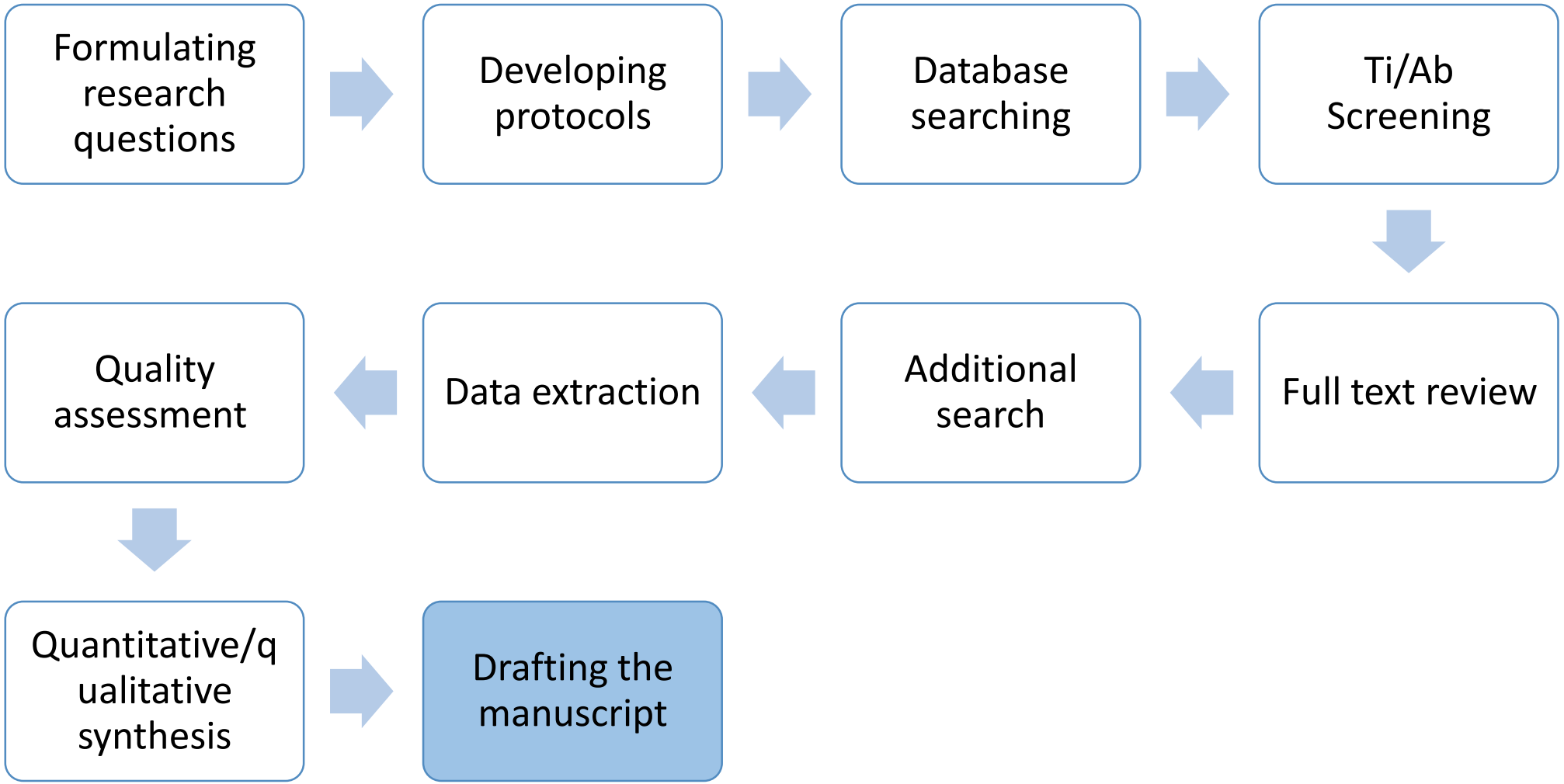


- **Fig 3. Summarized findings on social media outcomes.** (A) patient and caregiver focused objectives[1,2,3]; (B) Authors' conclusions on social media use with regard to patient and caregiver focused objectives[1,2,4]. [1]Adapted from Coulter and Ellins, 2007; [2]Only the main study objective was recorded from a single study; [3]More than one outcome category could be recorded from a single study; [4]Only one overall conclusion was recorded from each study. Frequency indicated by color: red, very frequent; yellow, moderately frequent; green, infrequent. N, number of studies.
- Impact of social media interventions and tools among informal caregivers of critically ill patients after patient admission to the intensive care unit: A scoping review

Sum Up- Any Questions?

- Quantitative synthesis – Meta-analysis
- Qualitative synthesis – Narrative synthesis

Summary Steps of Systematic Review



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	

Artificial Intelligence for Hip Fracture Detection and Outcome Prediction

A Systematic Review and Meta-analysis

INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	

Introduction

The number of artificial intelligence (AI) algorithms in the medical literature and health care industry is increasing rapidly. This increase is due to relatively recent advances in computational power, data accessibility, and model complexity through mathematical and computer science research.[1,2] Correspondingly, there has been an increasing number of AI algorithms and AI-enabled medical devices approved by the US Food and Drug Administration (79 and 343, respectively).[3-5] There are a large number of potential applications for AI; however, most of the models developed have focused on the interpretation of medical imaging and clinical decision support systems.[3] Across the literature, AI models are beginning to show the ability to automate and potentially improve clinicians' diagnostic and clinical decision-making.[6,7] However, preceding research and literature reviews have predominantly been conducted in the fields of radiology, pathology, oncology, and ophthalmology, with a smaller proportion of research being conducted within the surgical specialties and particularly orthopedic surgery.[6-10]

The most prominent domain within orthopedic surgery in which AI research has been conducted is in hip fractures. Among elderly populations, hip fractures make up more than 14% of total fractures, although they represent a disproportionate 72% of fracture-related health care costs.[11,12] Approximately 300 000 hip fractures occur per year in the US alone.[13,14] Despite prevention efforts, this number is steadily increasing due to an aging population.[13,15,16] Worldwide, this number is expected to reach 6.3 million hip fractures at a cost of $131.5 billion per year by 2050.[17,18] In addition to their significant prevalence and economic impact, hip fractures are also associated with significant individual morbidity and mortality, with a 1-year mortality rate of approximately 25% to 30%.[19-22] Therefore, technology to improve the efficiency of managing this condition has the potential to improve patient outcomes and provide economic benefit to health care systems.

Improvement of the efficiency of hip fracture diagnosis and surgery has received considerable attention in recent years. Expedited management and comprehensive care pathways have been proven to improve outcomes, including survival rate, for these patients.[22-24] These circumstances provide an ideal use case for this novel technology should its performance be equal or superior to human performance. Image analysis and clinical decision support systems powered by AI may automate sections of the diagnostic pathway and improve outcome prediction accuracy.[6-8] Expedited diagnosis by leveraging this technology would lead to rapid diagnosis and access to surgical care. Perioperative risk stratification for clinicians and hospitals caring for these patients can assist in decision-making, accurate expectation management, and financial and resource planning. Moreover, these applications have the potential to reduce errors secondary to physician fatigue from repetitive cognitive demands and improve informed decision-making for patients and families.[25-27] In this systematic review, we sought to evaluate the literature and performance of AI algorithms designed to improve the management of hip fractures in elderly patients across 2 domains: (1) to evaluate the performance of AI compared with health care professionals for detection of hip fractures on medical imaging and (2) to determine the accuracy of AI at predicting various postoperative clinical outcomes compared with traditional statistical methods.

METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	

Methods

Search Strategy and Study Selection

A systematic review of the literature was performed using MEDLINE, Embase, and the Cochrane Library for all articles published from database inception to January 23, 2023. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 reporting guideline was used to design the review.[28] The inclusion criteria and analysis plan were decided a priori and registered on PROSPERO (CRD42022351255). In each database, the following keywords were combined to identify relevant articles: *hip* OR *neck of femur* OR *femoral neck* OR *intertrochanteric* OR *pertrochanteric* OR *subtrochanteric* AND *fracture* OR *broken* AND *artificial intelligence* OR *AI* OR *machine learning* OR *ML* OR *computer vision* OR *neural network*. A manual reference search of included articles was also undertaken to identify any additional relevant articles. This review had 2 groups: (1) studies that developed any machine learning (ML) or deep learning model for the diagnosis of hip fractures using medical imaging and (2) studies that developed a model designed to predict any postoperative patient outcome following hip fracture surgery.

Eligibility Criteria and Data Extraction

Artificial intelligence models evaluating the radiographic diagnosis or outcome prediction of hip fractures, including femoral neck, intertrochanteric, and subtrochanteric fractures, were included, with isolated fractures of any other anatomical site being excluded (acetabular, pelvic, femoral head, midshaft femur, or distal femoral fractures). Studies designed to diagnose hip fractures from medical imaging were included if they were based on anteroposterior and lateral hip or anteroposterior pelvic plain radiographs. Ground truth must have been based on image review by a consensus medical expert group, radiologist report and image review by a staff radiologist, surgical confirmation, or cross-sectional imaging (computed tomography or magnetic resonance imaging) confirmation. All level 3 or higher studies, including randomized clinical trials, prospective studies, and retrospective studies, were included. Studies were not excluded based on the presence or absence of a comparator group or language of publication. Case reports, literature reviews, abstracts, unpublished studies, and nonhuman studies were excluded. Authors were contacted if needed to retrieve copies of unavailable manuscripts.

Screening of search results based on titles and abstracts was performed by 2 independent reviewers (J.D.M. and R.K.), with conflicts resolved by inclusion of a third reviewer (J.R.L.). Three reviewers independently assessed the eligibility following abstract screening for study inclusion according to the inclusion and exclusion criteria. In cases of conflict, decisions were made through consensus agreement among the 3 reviewers. Eligible full-text articles were evaluated, and relevant data were extracted independently by 2 reviewers (J.D.M. and R.K.) using a template data extraction form, with conflicts resolved by inclusion of a third reviewer (J.R.L.).

Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

Statistical Analysis

Odds ratios (ORs) with 95% CIs were used for dichotomous outcome measures. Heterogeneity was assessed using the I^2 statistic, with $I^2 \geq 75\%$ indicating considerable heterogeneity. A random-effects model to pool the data was planned to be used if considerable heterogeneity was found ($I^2 \geq 50\%$); otherwise, a fixed-effect model and a Mantel-Haenszel statistical method were used. Sensitivity and specificity of the diagnostic AI model's performance were plotted and compared with the performance of medical experts, with a pooled 95% CI around the mean. Youden index scores were calculated from sensitivity and specificity when reported. The area under the curve (AUC) of each predictive statistical and AI model were compared using a 2-tailed, unpaired *t* test. Microsoft Excel (Microsoft Corp) was used to extract data. For pooled data analysis, Review Manager (RevMan), version 5.4 (The Cochrane Collaboration) and Stata software, version 16.1 (StataCorp LLC) were used.

RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	

Results

Study Selection

Of 39 studies that met all criteria and were included in this analysis, 18 studies[29-46] (46.2%) used AI models to diagnose hip fractures on plain radiographs and 21 studies[47-67] (53.8%) used AI models to predict patient outcomes following hip fracture surgery. A PRISMA flowchart of included studies is displayed in eFigure 1 in **Supplement 1**. The characteristics of the included studies are given in **Table 1** (diagnostic studies) and **Table 2** (outcome prediction studies). Diagnostic studies were published between 2019 and 2022 and used a total of 39 598 plain radiographs to train, validate, and test AI models (**Table 1**; eTable 1 in **Supplement 1**). Outcome prediction studies were published between 2004 and 2022. Mortality followed by length of hospital stay were the most commonly predicted outcomes, with other predicted outcomes of 30-day complications, living situation, postoperative delirium, and modified functional independence measure.[47,58,61] A pooled total of 714 939 hip fractures were used for training, validating, and testing ML models specific to postoperative outcome prediction. All databases used for outcome prediction are listed in eTable 2 in **Supplement 1**.

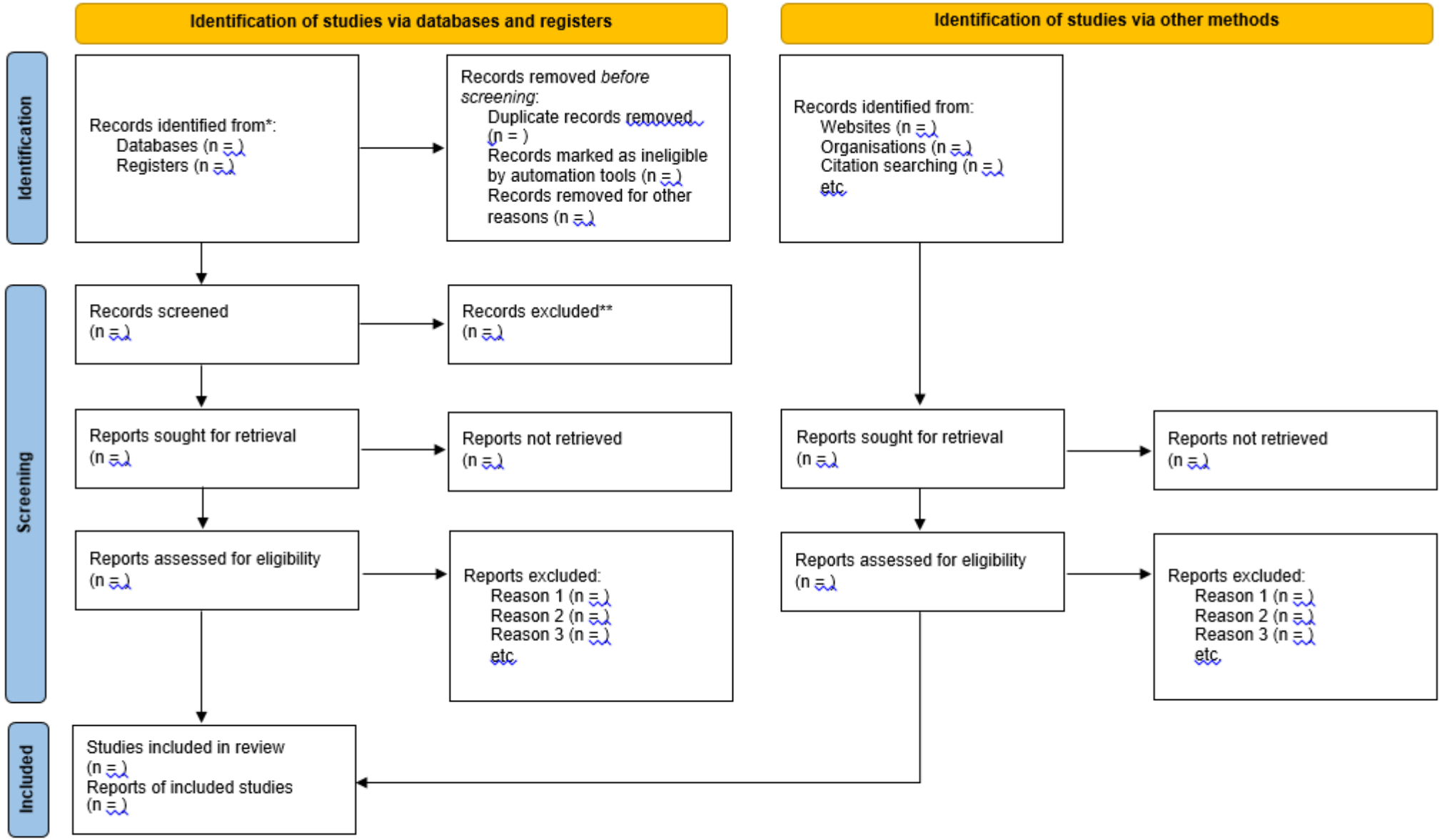
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	

Table 1. Included Studies on Application of Artificial Intelligence for Diagnosis of Hip Fractures

Source (country)	Input imaging	No. of output classes	Output	Algorithm used	No. of radiographs	Training size, %	Validation size, %	Testing size, No. or %	Ground truth
Cheng et al,[29] 2019 (Taiwan)	AP pelvic radiograph	2	Fractured (femoral neck and trochanteric); nonfractured	DCNN	3605	80	20	100	Radiologist report or CT report with each image reviewed by trauma surgeon
Urakawa et al,[30] 2019 (Japan)	AP proximal femoral radiograph	2	Fractured (intertrochanteric); nonfractured	CNN	3346	80	10	10%	Surgically confirmed
Adams et al,[31] 2019 (Australia)	AP hip cropped from AP pelvic radiograph	2	Fractured (femoral neck); nonfractured	AlexNet DCNN; GoogLeNet DCNN	640	80	20	160	Surgically confirmed
Mawatari et al,[32] 2020 (Japan)	Pelvic radiograph	2	Fractured (proximal femur fracture); nonfractured	DCNN	352	85.8	NR	14.2%	CT or MRI confirmed
Jiménez-Sánchez et al,[33] 2020 (Germany, Spain, and France)	AP and lateral pelvic radiograph, images were cropped	2	Fractured; nonfractured	ResNet-50; AlexNet	1347	70	10	20%	Image review by group of experts (1 staff trauma surgeon, 1 staff radiologist, 1 senior trauma resident)
		3	AO type A fracture; AO type B fracture; nonfractured	ResNet-50; AlexNet					
Yu et al,[34] 2020 (US)	AP hip radiograph	2	Fractured; nonfractured	DCNN	627	60	20	20%	Surgically confirmed or CT confirmed
Kitamura,[35] 2020 (US)	Pelvic radiograph	2	Normal; abnormal	Densenet-121 architecture	7337	70	NR	30%	Radiologist report and image review by a staff radiologist
		8	Normal; anterior pelvis; posterior pelvis; pelvic ring; proximal femur; acetabular; femur/acetabular; nonfemoral						
Krogue et al,[36] 2020 (US)	Hip and pelvic radiograph, hips were labeled via bounding boxes	6	Normal; displaced femoral neck fracture; nondisplaced femoral neck fracture; intertrochanteric fracture; previous open reduction and internal fixation; previous arthroplasty	DCNN (DenseNet)	1999	61.1	24.4	14.5%	Consensus by experts; CT, MRI, postoperative imaging in the event of uncertainty
		2	Fractured; nonfractured						
Yamada et al,[37] 2020 (Japan)	AP and lateral pelvic radiograph	3	Femoral neck fractures; trochanteric fractures; nonfractured	CNN	2923	89.7	10.3	NR	Consensus by experts and CT
Mutasa et al,[38] 2020 (US)	AP pelvic radiograph	2	Femoral neck fracture (any Garden fracture); normal	CNN	1063	Unclear	20	Unclear	Image review by a single staff radiologist
		3	Femoral neck fracture (Garden I/II fracture); femoral neck fracture (Garden III/IV fracture); normal						
Beyaz et al,[39] 2020 (Turkey)	AP hip cropped from AP pelvic radiograph, various image sizes assessed	2	Fractured (femoral neck); nonfractured	CNN; GA	234	NR	NR	NR	Unclear
Açıcı et al,[40] 2021 (Turkey)	AP pelvic radiograph	2	Fractured (femoral neck); nonfractured	CNN; GA; PSO; LSTM; BILSTM	64	NR	NR	NR	Unclear
Bae et al,[41] 2021 (Korea)	AP pelvic radiograph	3	Displaced fracture; nondisplaced fracture; nonfractured	CNN; ResNet 18 with CBAM	4189	80	10	10%	CT or MRI confirmed
Cheng et al,[42] 2021 (Taiwan)	AP pelvic radiograph	3	Hip fracture only; pelvic fracture only; no acute finding	PelviXNet (DenseNets + FPN); CNN	5204	100	NR	1888	Image review by group of clinicians
Guy et al,[43] 2021 (France)	AP and lateral pelvic radiograph	3	Femoral neck fracture; trochanteric fracture; nonfractured	Tensorflow deep learning algorithm	1309	80	10	10%	Unclear
Twinprai et al,[44] 2022 (Thailand)	AP hip and pelvic radiograph	2	Fractured; nonfractured	DCNN	1000	90	NR	10%	Consensus by experts and CT/MRI
		3	No fracture; trochanteric; intracapsular						
Murphy et al,[45] 2022 (UK)	AP pelvic radiograph	4	Normal; femoral neck fracture; intertrochanteric fracture; subtrochanteric fracture	CNN	3659	60	20	20%	Consensus by experts
Liu et al,[46] 2022 (China)	AP hip radiograph	2	Nonfractured; fractured (intertrochanteric)	Faster RCNN	700	91.9	NR	8.1%	Unclear

Abbreviations: AO, atlanto-occipital; AP, anteroposterior; BILSTM, bidirectional long short-term memory; CBAM, convolutional block attention module; CNN, convolutional neural network; CT, computed tomography; DCNN, deep convolutional neural network; FPN, feature pyramid network; GA, general algorithm; LSTM, long short-term memory; MRI, magnetic resonance imaging; NR, not reported; PSO, particle swarm optimization; RCNN, region-based convolutional neural network.

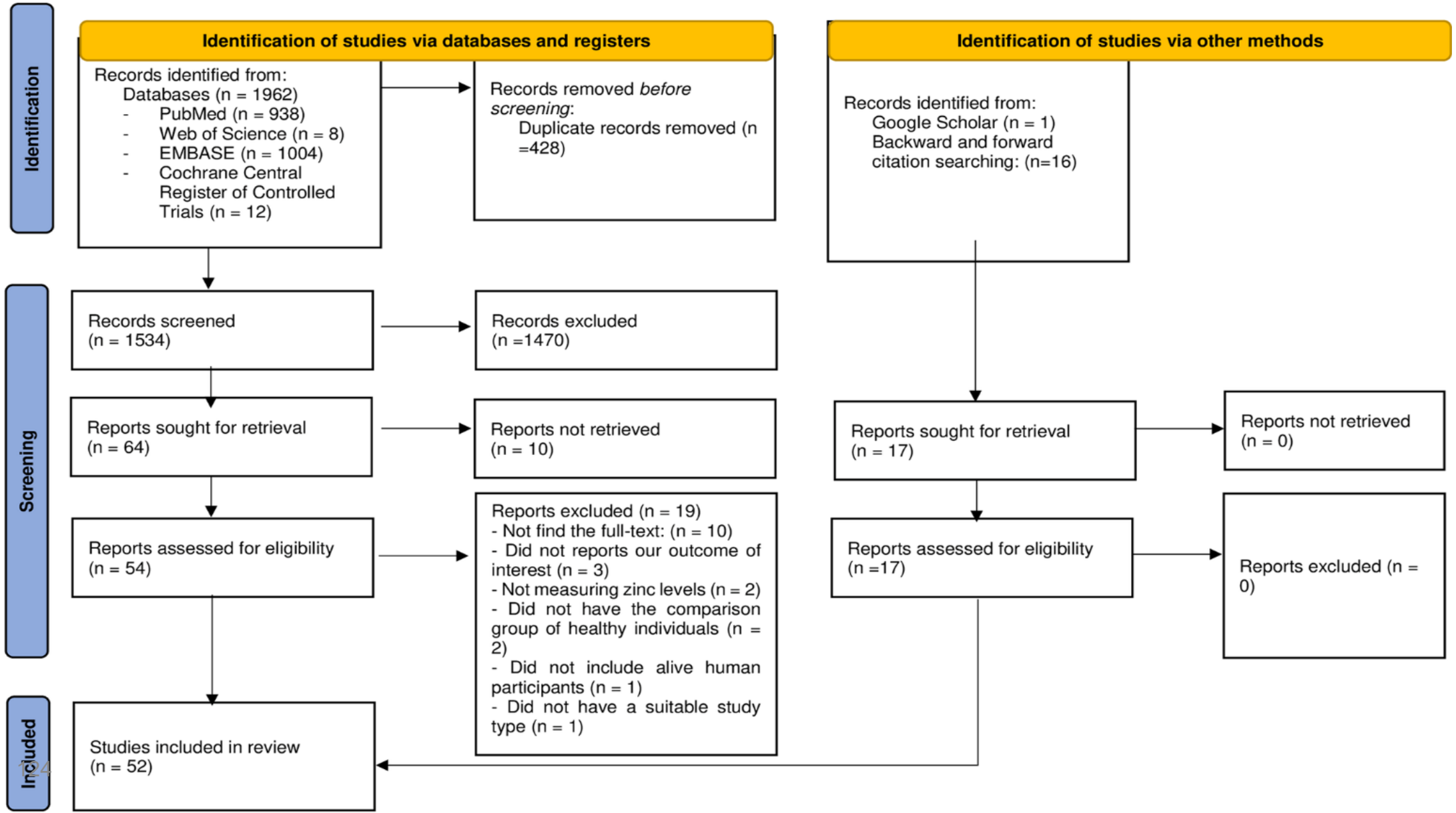
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*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.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

PRISMA Flowchart Example



Study Characteristics Table Example

Table 1. Baseline Characteristics of the Studies Included in the Meta-analysis

Source	Study design (trial registration No.)	Study population	Type of CBD	Total daily CBD dose	Length of treatment	Safety follow-up duration	Sample size, No.	CBD, No.	Placebo, No.	Male, No. (%)	Female, No. (%)	Age, mean (SD), y
Ben-Menachem et al,[74] 2020	Phase 2, 2-arm, parallel-group, double-blind, randomized, placebo-controlled DDI trial (NCT02607891)	Patients with epilepsy from Spain, the Netherlands, and Sweden, aged 16-55 y, already receiving a stable dose of stiripentol or valproate and having experienced at least 1 countable seizure of any type within the last 2 mo	Provided by GW Pharmaceuticals (100 mg/mL of oral solution)	20 mg/kg	24 d	NA	34	28	6	CBD: 17[62]; placebo: 5[84]	CBD: 11[40]; placebo: 1[18]	CBD: 30.1 (11.1); placebo: 26.9 (7.0)
Devinsky et al,[75] 2017	Randomized, double-blind, placebo-controlled trial (NCT02091375)	Children and young adults from the US and Europe, aged 2-18 y, with poorly controlled Dravet syndrome	Provided by GW Pharmaceuticals (100 mg/mL of oral solution)	20 mg/kg	14 wk	4 wk	120	61	59	CBD: 35[58]; placebo: 27[47]	CBD: 26[44]; placebo: 32[55]	CBD: 9.8 (4.8); placebo: 9.7 (4.7)
Devinsky et al,[76] 2018	Phase 3, randomized, double-blind, placebo-controlled trial (NCT02224560)	Patients with Lennox-Gastaut syndrome from the US, Spain, UK, and France, aged 2-55 y, with at least 2 types of generalized seizures, including drop seizures, for at least 6 mo	Provided by GW Pharmaceuticals (100 mg/mL of oral solution)	10, 20 mg/kg	14 wk	4 wk	225	Total: 149; CBD 10 mg/kg: 73; CBD 20 mg/kg: 76	76	CBD: 85[58]; placebo: 44[59]	CBD: 64[44]; placebo: 32[43]	CBD 10 mg/kg: 15.4 (9.5); CBD 20 mg/kg: 16.0 (10.8); placebo: 15.3 (9.3)
Devinsky et al,[77] 2018	Randomized, double-blind, placebo-controlled, parallel-group trial (NCT02091206)	Patients with Dravet syndrome from the US and UK, aged 4-10 y, taking at least 1 AED	Provided by GW Pharmaceuticals (25 or 100 mg/mL of oral solution)	5, 10, 20 mg/kg	3 wk	4 wk	34	Total: 27; CBD 5 mg/kg: 10; CBD 10 mg/kg: 8; CBD 20 mg/kg: 9	7	CBD: 11[42]; placebo: 5[72]	CBD: 16[60]; placebo: 2[29]	CBD 5 mg/kg: 7.2 (1.9); CBD 10 mg/kg: 7.4 (2.1); CBD 20 mg/kg: 8.7 (1.8); placebo: 7.0 (0.9)

DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	

Limitations

To our knowledge, this study was the first evaluation of the literature surrounding AI algorithms developed for the management of hip fractures from diagnosis to postoperative outcomes. This review provides insight into the potential impact that applying AI has on the management of one of the most common, resource-intensive, and devastating diagnoses. Nonetheless, there are limitations to the algorithms and methods of included studies, as mentioned previously, as well as to our review. A hierarchal summary receiver operating curve summarizing performance across all studies was unable to be created because studies did not report data in the form of a contingency table. Various AI techniques and predictive features were used across all studies, but we were unable to compare the use of each strategy and the effect this had on algorithm performance due to data and study reporting heterogeneity. Additionally, the quality of studies was unable to be properly evaluated because the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis for Artificial Intelligence (TRIPOD-AI) guidelines are still under development.[75]

DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	

Conclusions

This systematic review and meta-analysis helps evaluate the literature surrounding the current development of AI applications for the management of hip fractures. The potential applications regarding the use of AI to aid with diagnosis from hip and pelvic radiographs are promising. However, the use of AI does not seem to provide substantial additional benefit over traditional multivariable predictive statistics. The results of these applications are variable, which may be due to the quality or quantity of data from which these algorithms are developed rather than a true limitation of AI's power. Further studies should focus on evaluating whether these limitations remain with the use of large, accurate, multi-institutional data sets. Moreover, studies externally validating and implementing hip fracture diagnostic algorithms need to be performed to assess the effect on patient care.

OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Conflict of Interest Disclosures: Dr Lex reported receiving grants from Arthrex Inc outside the submitted work and serving on the Resident Advisory Board for PrecisionOS Technologies. No other disclosures were reported.

Funding/Support: Scholarship support for this project (specifically for Dr Lex) was provided by the William and Suzanne Holland Chair in Musculoskeletal Research and the Queen Elizabeth II/Patty Rigby & John Wedge Graduate Scholarships in Science and Technology.

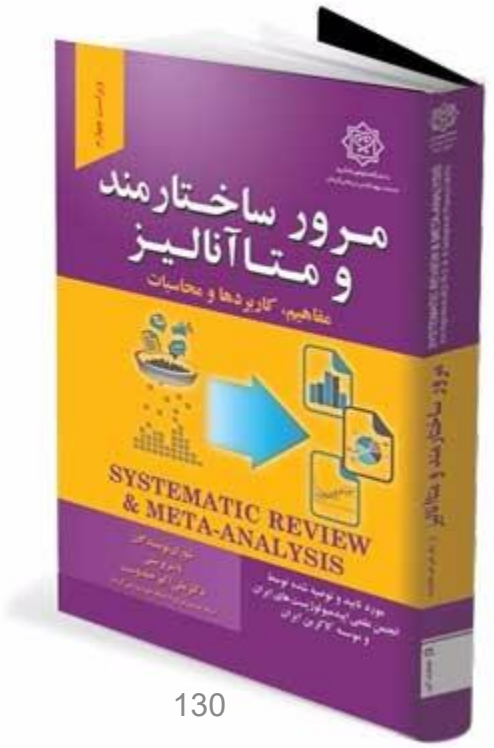
Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

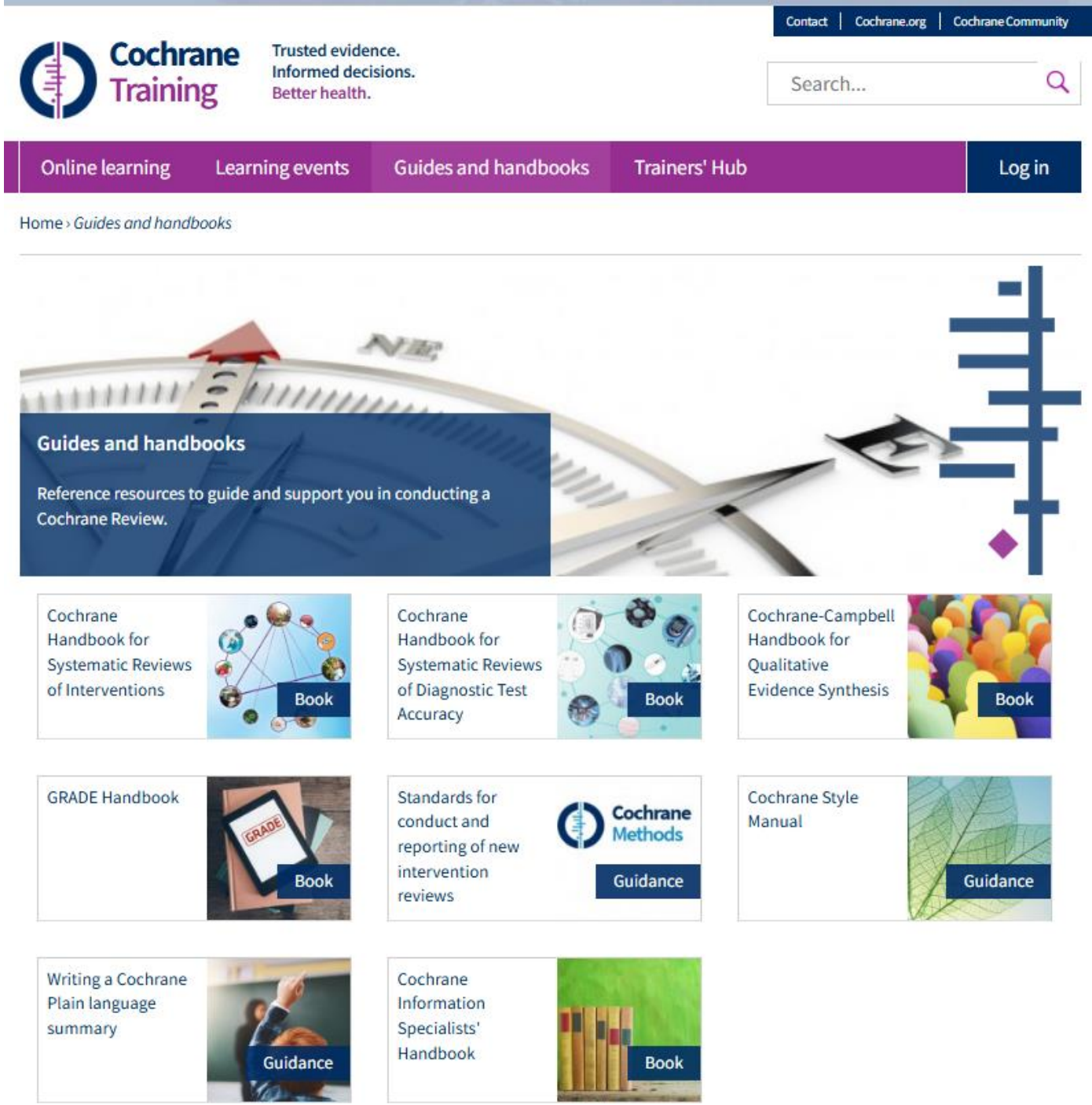
Sum Up- Any Questions?

- PRISMA 2020 checklist and statement
- PRISMA flowchart
- Study characteristics table

References

- https://training.cochrane.org/handbooks
  - مرور ساختارمند و متاآنالیز؛ویراست جدید:چهارم/مرجع





Overview and take-home messages