In Search of Better Health

Evidence Synthesis:
Reproducibility and Interpretation

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Outline

- Part 1:
  - Define evidence synthesis, reviews
  - Define systematic review and outline steps
  - Define meta-analysis and the process
- Part 2:
  - Outline FAIR principles and application to SR process
  - Challenges in evidence synthesis
  - Barriers to implementing FAIR principles
  - Role of Artificial intelligence in Systematic review process

Systematic Review Process

Part 1

Evidence synthesis

- Evidence synthesis refers to a method that identifies, selects and combines results from multiple studies.
  - Includes reviews
  - Systematic review is considered the cornerstone of evidence synthesis

Reviews

- A review is a summary or synthesis of more than one study
- Several types of reviews available, eg:
  - Narrative reviews, scoping reviews, rapid reviews, systematic reviews, umbrella reviews
- Reviews differ by rationale, methodological rigor and risk of bias
- A good review is a readable summary of ALL the evidence, unbiased, transparent, replicable and up-to-date

Need for reviews

Narrative Reviews

- Summaries of evidence on a given topic—usually written by an expert in the field
- Also known as a literature review or traditional review
- Typically, involves informal and subjective methods to collect and interpret information
- Problems with narrative reviews
  - Personal bias
  - Publication bias
  - Language bias
  - Small sample size
- Strictly speaking, NOT considered a type of evidence synthesis

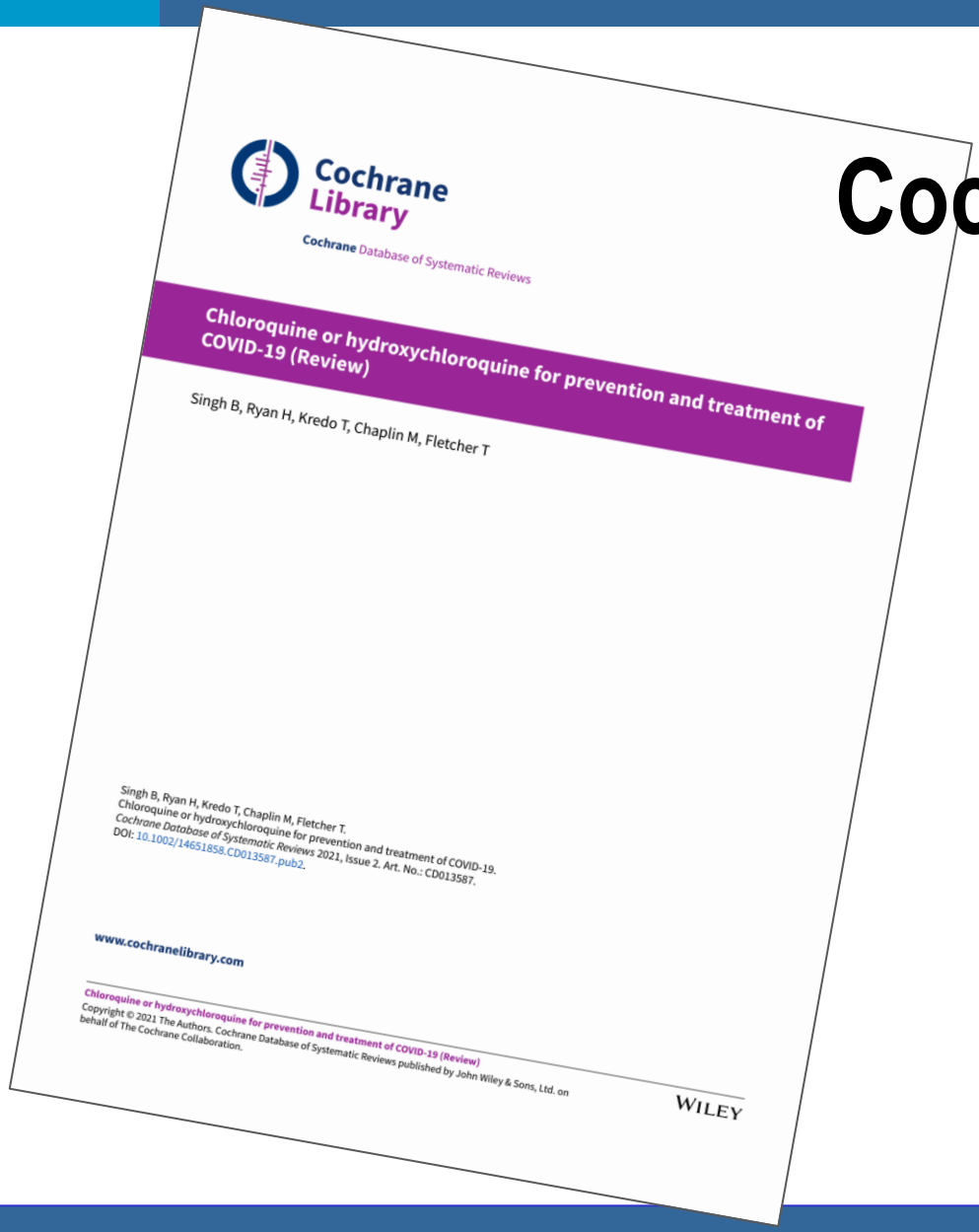
Rapid Reviews

- A form of knowledge synthesis that accelerates the process of conducting a systematic review through streamlining or omitting specific methods to produce evidence for stakeholders in a timely and resource-efficient manner
- Useful for public health emergencies (eg COVID, Mpox, climate change)
- The process is shortened by:
  - Limited scope of review question
  - Limiting search by years, databases, language and sources beyond electronic searches
  - Single rather than two reviewers for some review steps (eg title and abstract review, full text review, methodological quality assessment and data extraction process)
  - Limited risk of bias assessment
  - Qualitative summary rather than meta-analysis
  - Fast-tracking of PROSPERO registration

Scoping Reviews

A form of literature review which follows a similar process to a systematic review, but which is performed to rapidly outline the breadth, depth and type of literature available pertaining to a certain topic and or the key constructs underpinning it.

- Answer broad questions while maintaining the same Methodological rigour as a systematic review
- Aims to identify and map the available evidence for a specific area
- Usually done to determine the need for a systematic review



Cochrane reviews

A systematic review produced by the Cochrane Collaboration

- Presented in a standardised format
- Extensive peer review
- Published electronically on CL
- Kept up-to-date

Quality and reporting, on average, are better than other systematic reviews … but not without flaws!

Meta-analysis

- Meta-analysis is a statistical procedure that integrates (pools) the results of several independent studies considered to be “combinable.”
- Several types exist, such as:
  - Individual-patient data meta-analysis
  - Network meta-analysis
  - Bayesian meta-analysis

References with more review types

REVIEW ARTICLE

Review Typology: The Basic Types of Reviews for Synthesizing Evidence for the Purpose of Knowledge Translation

Sunil Sadruddin Samnani[1], Marcus Vaska[2], Salim Ahmed[1] and Tanvir C. Turin[1]

Review Article

A typology of reviews: an analysis of 14 review types and associated methodologies

Maria J. Grant* & Andrew Booth†, *Salford Centre for Nursing, Midwifery and Collaborative Research (SCNMCR), University of Salford, Salford, UK, †School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

Review Article

Meeting the review family: exploring review types and associated information retrieval requirements

Anthea Sutton*  , Mark Clowes, Louise Preston & Andrew Booth
School of Health and Related Research (ScHARR), The University of Sheffield, Sheffield, UK

What is a systematic review?

"A review in which **bias** has been reduced by :

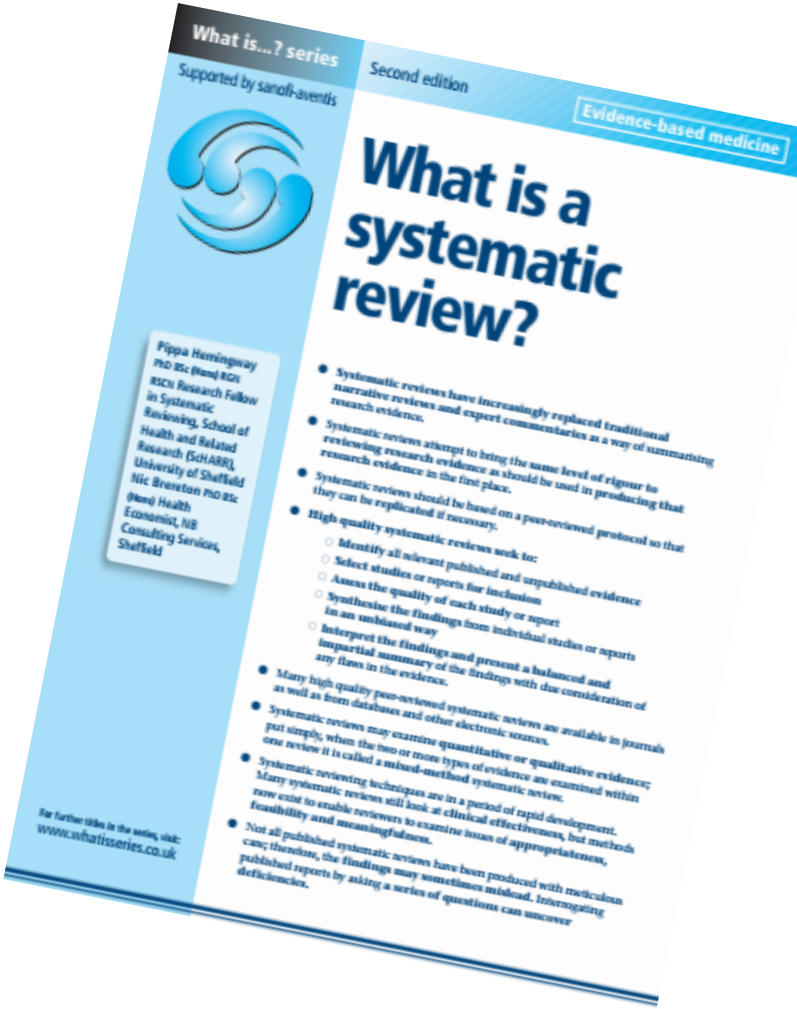
the systematic identification

Critical appraisal

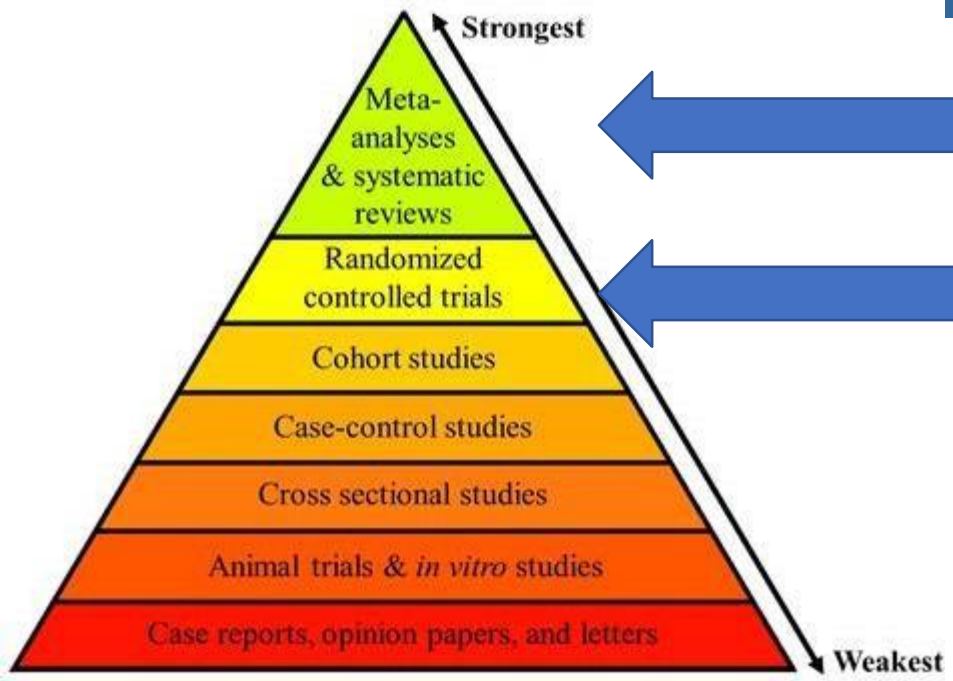
Synthesis, and,

If relevant, statistical aggregation

of all relevant studies on a specific topic according to a predetermined and explicit method."



Hierarchy of scientific evidence



Systematic reviews of RCTs are higher level of evidence, as based on more than one RCT

Randomised controlled trials (RCTs) of interventions give best quality as a single study

- **Different study designs have different reliability/quality of evidence**

Why we need systematic reviews

- Information overload
  - Integration of information for decision making
- Cheaper and quicker source of evidence
- Generalizability of findings can be established
- Consistency of intervention effects can be assessed
  - Inconsistencies and conflicts in data can be explained
- Increased statistical power from increased sample size
  - Improved precision of intervention effects from large sample size
- Reduced bias (systematic and random) by explicit methods

Systematic review process

- Formulate (a) Review Question(s)
- Develop a review protocol
- Define the inclusion and exclusion criteria
  - PICO, PECO, SPIDER, SPICE
- Search the literature and select relevant studies
- Assess the risk of bias/methodological quality of studies
- Extract data
- Synthesise/summarise the evidence using appropriate methods
  - Qualitative Summary
  - Meta-analysis (if possible)
- Develop a structured report of the review

Before you start

- Check the systematic review registry to confirm that your planned review has not yet been done
  - To avoid duplication of efforts
  - To decide that the reviews are so different that there is no duplication
- If you find an existing similar published systematic review, assess it for:
  - Which interventions/comparisons were assessed?
  - In which populations?
  - What were the effects of the interventions?
  - What is the gap in the evidence?

Be prepared

- A good review is the product of team effort
- Any review project requires:
  - Review question: defines your destination
  - Review protocol: details your proposed route and activities
  - Review team
- The review question and protocol guides the whole systematic review process

Review question

- Formulating a review question is a process
- A well-formulated question informs all the review steps:
  - Criteria to select studies (eligibility)
  - Development of search strategy
  - Data to be extracted
  - Interpretation of results
  - Summary of findings

Review question

Components of a review question: PICO

- P: Participants or populations
- I: Intervention
- C: Comparison group(s)
- O: Outcome

To formulate a review question, you need two or more of the above elements.

Eligibility criteria

- Based on PICO
- Criteria for considering studies
  - Types of studies (RCTs, other designs)
  - Types of participants (by age-group, diagnosis, setting)
  - Types of interventions (experimental, comparator)
  - Types of outcome measures (primary, secondary)

Biannual praziquantel for schistosomiasis

Example

Research Question:

- In populations at risk of schistosomiasis [P], is biannual preventive treatment with praziquantel [I] more effective at reducing prevalence and intensity of infection [O] compared to annual treatment [C]?

- **Population**:
  - Participants with schistosomiasis
- **Intervention:**
  - Biannual praziquantel treatment
- **Comparison group:**
  - Annual praziquantel treatment
- **Outcome**:
  - Reduction of schistosomiasis prevalence and intensity of infection

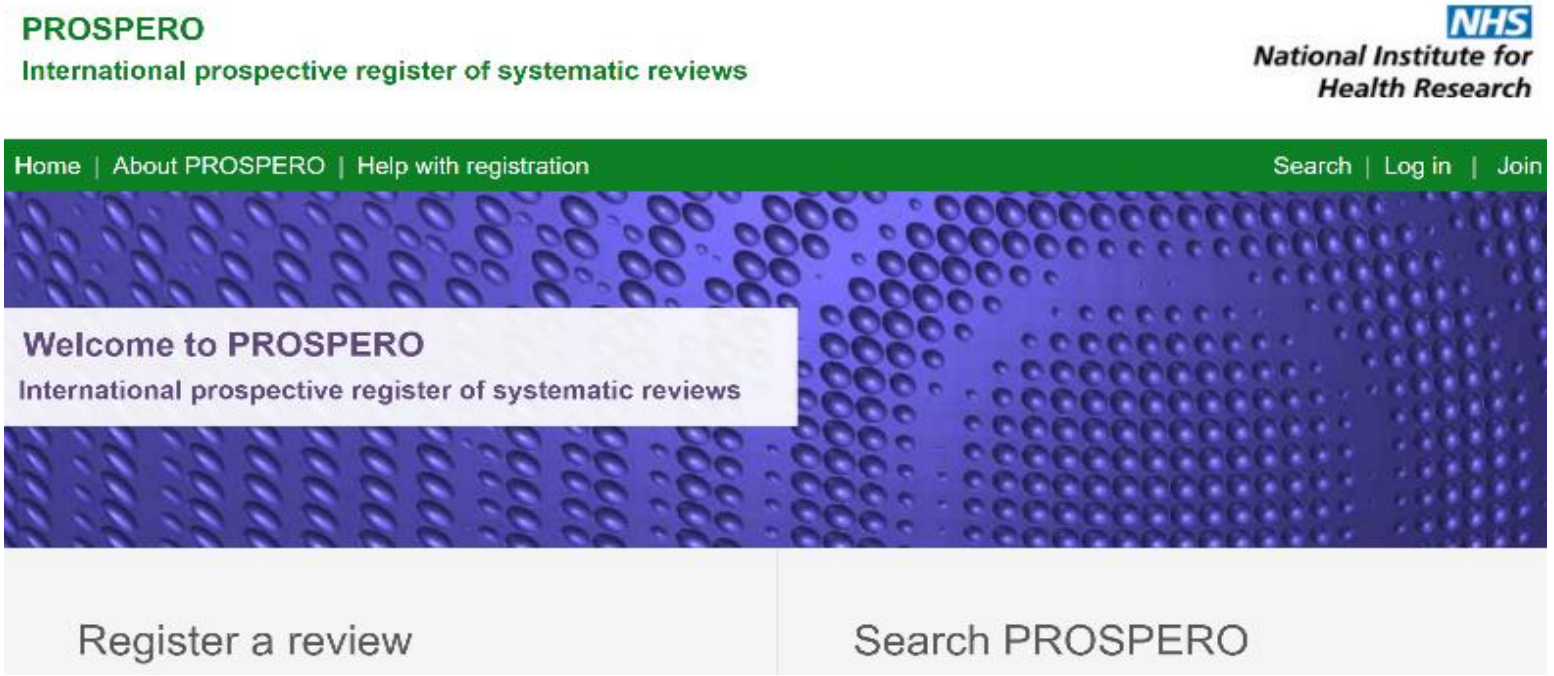
Review Protocol

- A protocol is an essential component of the review process
- Important to write in advance/in future tense
- Helps to think through the review and to avoid errors and biases (post hoc analysis)
- Outlines the background, objectives, and methods
- Follows the PRISMA outline
  - PRISMA=Preferred Reporting Items for Systematic reviews and Meta-Analysis
- Aim of review protocol:
  - To describe current evidence
  - To identify the review question
  - To outline/pre-specify methods to be used to

Why we need a review protocol

- Reduce the impact of bias
- Allow peer review
- Reduce duplication
- Plan tasks and allocate resources
- Ensures transparency/replication of methods
- Encourage collaboration
- Usually, required to publish or register the review protocol online (PROSPERO)

Protocol Registration



- Enables search for ongoing reviews
- Should register planned review online (& update as work progresses)
- Avoids duplication of reviews

Systematic Review process

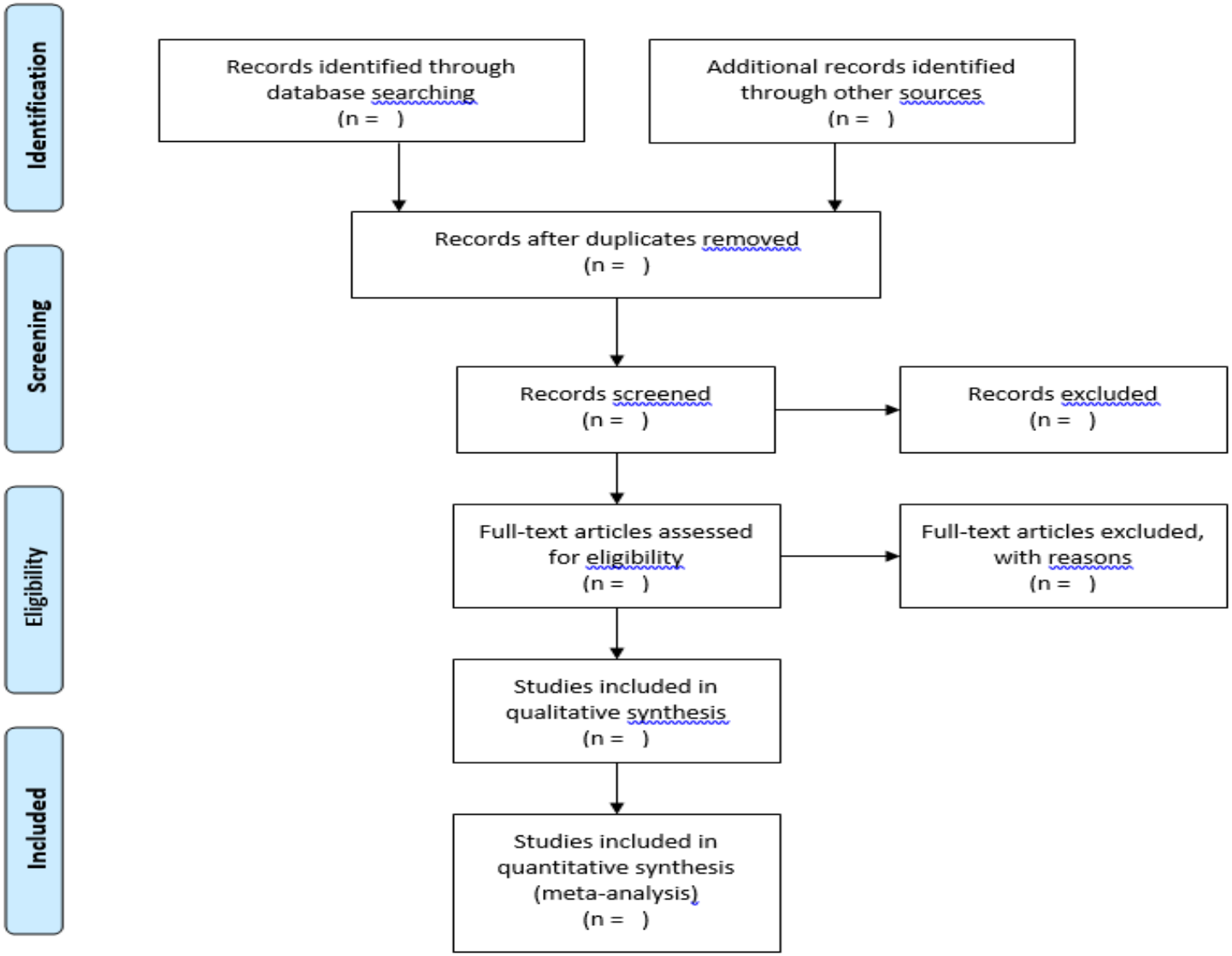
Search methods for the identification of studies

- Searching for studies
  - Plan the search process
    - Design search strategies
    - Involve a librarian or information scientist
  - Electronic database searches
    - Search more than one database (for a comprehensive search)
    - PubMed, MEDLINE, EMBASE, Scopus, Web of Science, CINAHL
    - Trial registries
    - Grey literature (conference abstracts)
  - Searching other resources
    - Reference lists of included studies
    - contacting experts for unpublished studies
  - Consider restrictions
    - Date limits, language, publication type, geographical limits, study quality
  - Managing references
    - EndNote, Zotero, Ryann, RefWorks, and Mendely
  - Always record the date of the last search

Systematic review process

- **Selecting studies**
  - Purpose is to screen the potentially eligible studies for eligibility
  - Done by at **least two authors**
  - Use the inclusion criteria developed from the review question
  - Screening of studies done in two stages:
    - Titles and abstracts (for irrelevant studies)
    - Full-text papers (for potentially eligible studies)
      - Should record a list of excluded studies and reasons for exclusion
  - Process can be done electronically (eg Covidence)
  - Should define in advance how disagreements will be resolved
      - Usually by discussion to reach consensus, or involve a third reviewer

Presentation of search and screening results



Risk of bias assessment

- Bias is a systematic deviation from the truth
- More concerned about systematic error (relates to internal validity)
- Risk of bias is the probability that bias is present
- An essential component of any systematic review process
  - Measures the methodological quality of included studies
  - Also known as critical appraisal of the studies
  - Several validated checklists/tools are available
- Assessed for each included study
- Should be assessed by at least 2 people independently
- Should define in advance how disagreements will be handled
- Some risk of bias assessment tools include:
  - Cochrane risk of bias (ROB) tool
  - Risk of bias for non-randomised studies (ROBIN tool)

Risk of bias -1 (RoB-1) tool

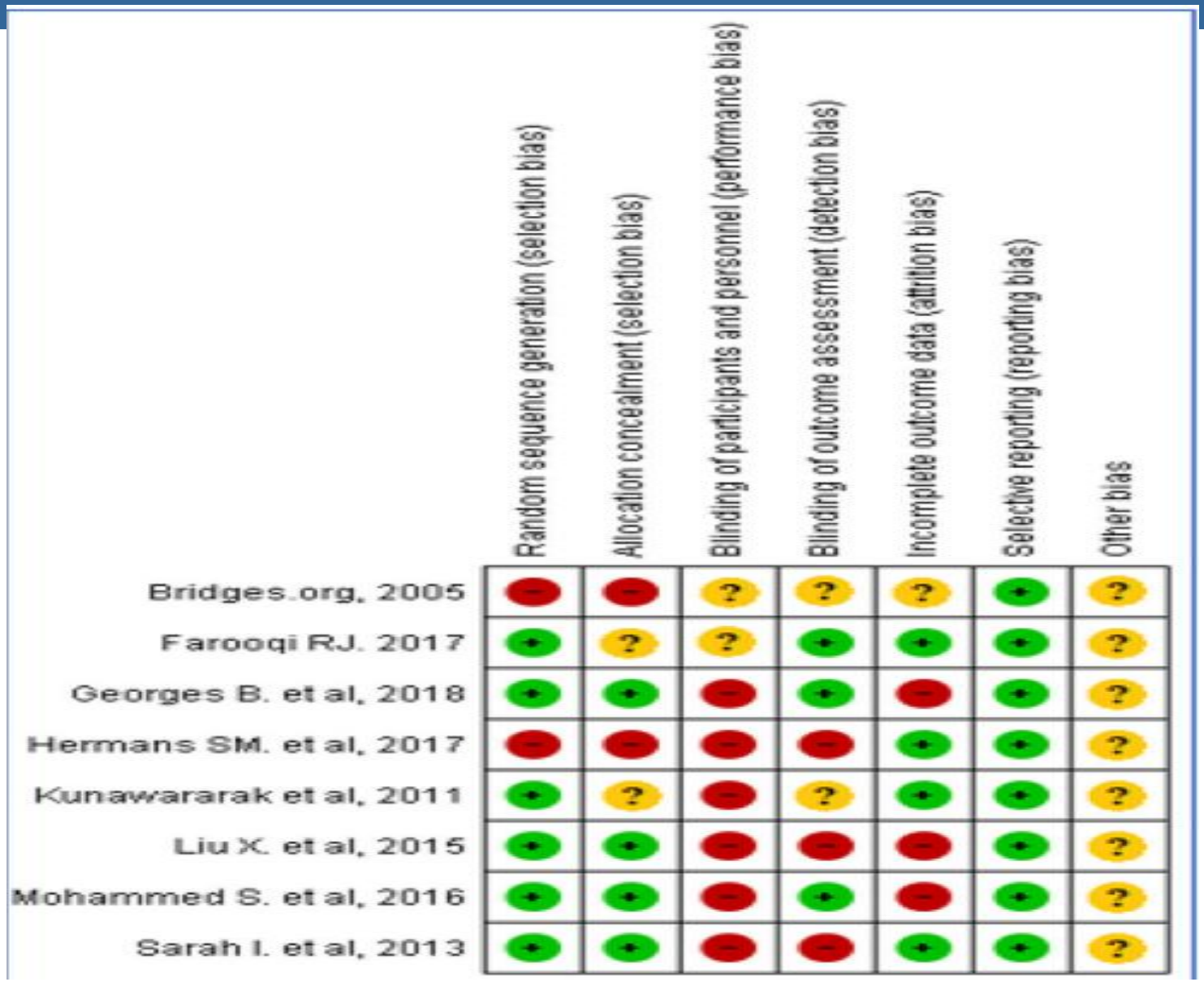
- Cochrane risk of bias tool 1
- Assess bias using six domains
  - Sequence generation (selection bias)
  - Allocation sequence concealment (selection bias)
  - Blinding of participants, personnel, and outcome assessors (performance/detection bias)
  - Incomplete outcome data (attrition bias)
  - Selective outcome reporting (reporting bias)
  - Other potential threats to validity

- Risk of bias assessment (scoring)
  - Low risk of bias
  - Unclear risk of bias
  - High risk of bias

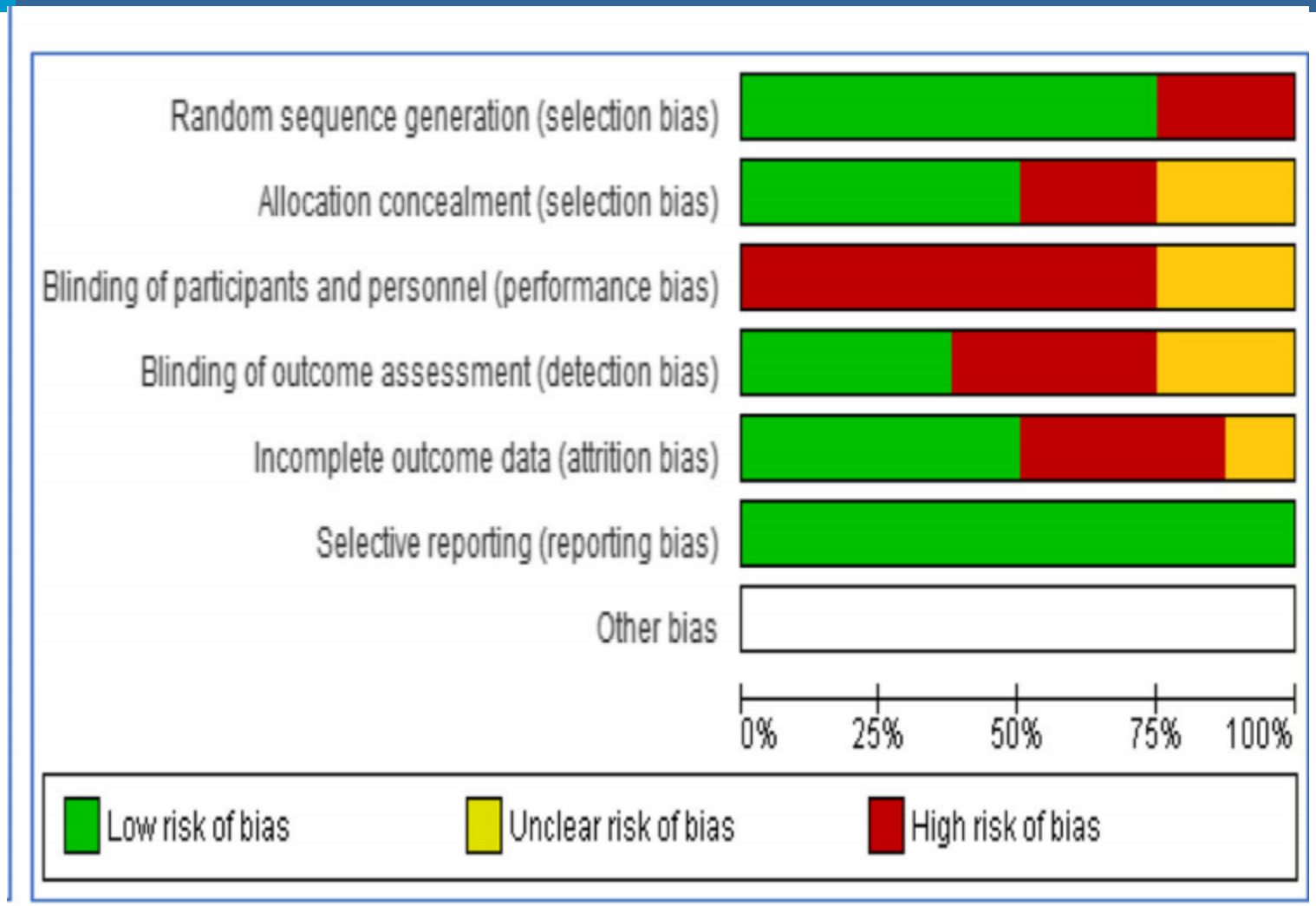
RoB-1 assessment criteria

Domain	**Criteria for judging**
Sequence generation	Was the allocation sequence adequately generated?
Allocation concealment	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors	Was knowledge of the allocated interventions adequately prevented during the study?
Incomplete outcome data	Were incomplete outcome data adequately addressed?
Selective outcome reporting	Are the reports of the study free of suggestion of selective outcome reporting?
Other potential threats to validity	Was the study free of other problems that could put it at risk of bias?

Risk of bias presentation (example)



Risk of bias summary graph (Example)



Systematic Review Process

Data extraction

- Information to be extracted from each study report
- Should be outlined in the review protocol
- Need a (piloted) data abstraction sheet
- Done by at **least 2 authors**
- Resolve disagreements

Systematic Review Process

Data analysis/synthesis

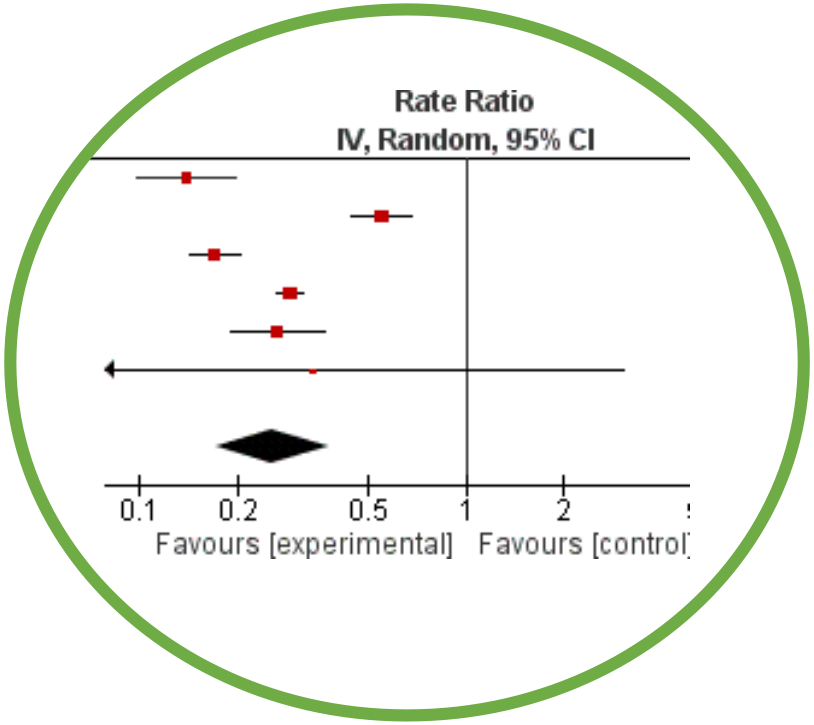
- Develop an analysis plan at the protocol stage
- If data is not combinable, describe qualitatively
- If data is combinable, consider meta-analysis
- Use software (eg RevMan, Stata, Meta-analyst)
- Establish the presence of heterogeneity
- Summary of the findings (use GRADE methodology)

Meta-analysis

- A statistical procedure that integrates the results of several independent studies considered to be “combinable.”
- Provides a quantitative summary of the overall treatment effect
  - a pooled estimate and confidence interval

Difference between systematic review and meta-analysis

- A systematic review answers a defined research question by collecting and summarizing all evidence based on pre-specified eligibility criteria.
- A meta-analysis is when statistical methods are used to summarise the results of studies.



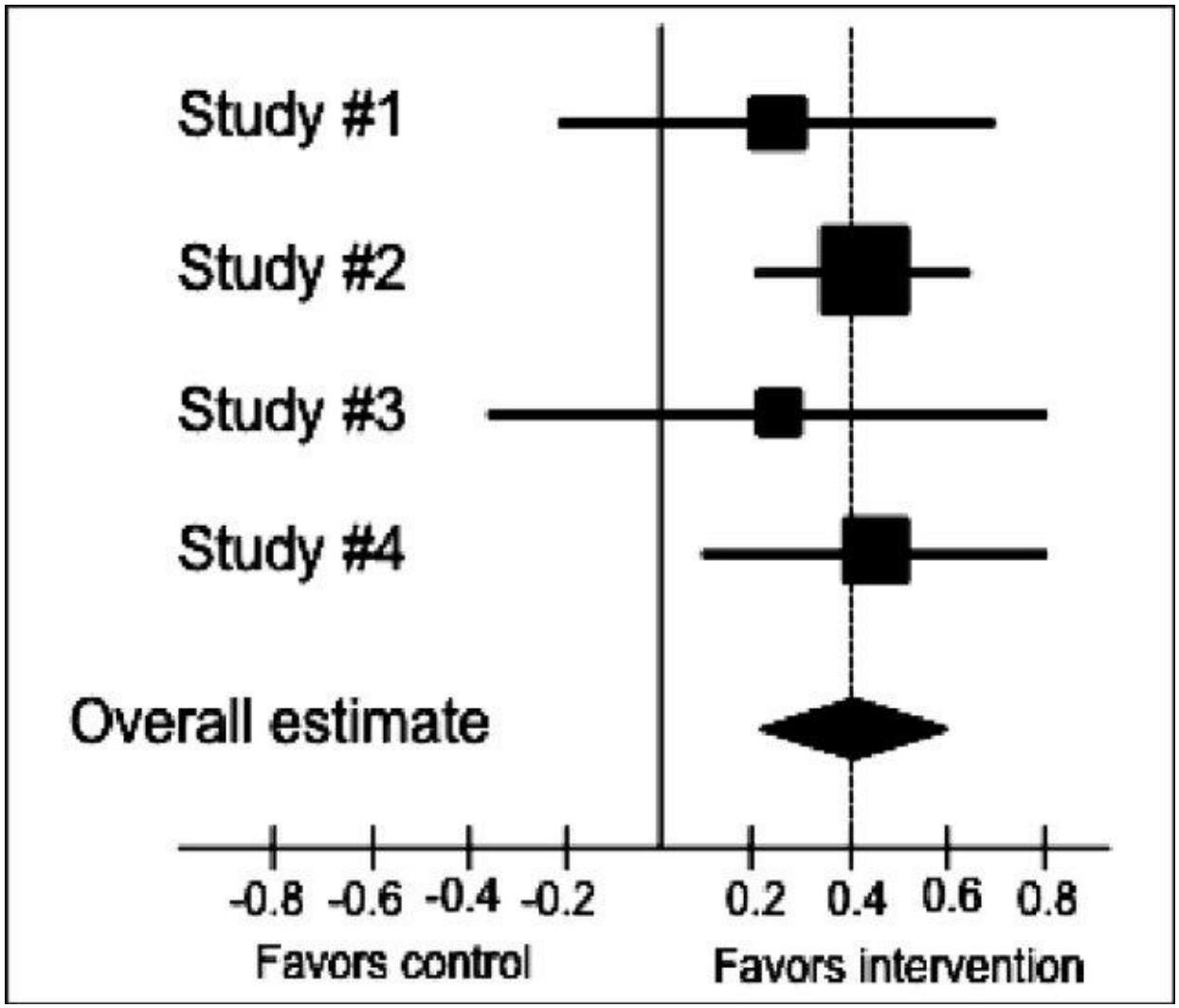
Why perform meta-analysis

- Quantify treatment effects and their uncertainty
- Increase power
- Increase precision
- Explore differences between studies
- Settle controversies from conflicting results
- Generate new hypotheses

Principles of meta-analysis

- Only possible in combinable studies
  - Homogeneity assumption (don't compare apples and oranges)
- Need more than one study
- Conducted in 2 stages:
  - summary measure of effect for each study
  - Combined summary measure of effect for all included studies
    - a weighted average of the effect
- Should incorporate statistical assumptions
  - Fixed effects
  - Random-effects
- Should take heterogeneity into account
- Presented as a forest plot

Forest plot


Study #1
Study #2
Study #3
Study #4
Overall estimate
-0.8 -0.6 -0.4 -0.2
0.2 0.4 0.6 0.8
Favors control
Favors intervention

Effect of SMS vs non-SMS on anti-TB treatment adherence

Study or Subgroup	SMS Events	SMS Total	Non-SMS Events	Non-SMS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bridges.org, 2005	161	221	153	221	6.4%	1.05 [0.93, 1.19]
Farooqi RJ. 2017	70	74	69	74	2.9%	1.01 [0.93, 1.10]
Georges B. et al, 2018	111	137	106	142	4.4%	1.09 [0.96, 1.23]
Hermans SM. et al, 2017	171	183	268	302	8.5%	1.05 [1.00, 1.11]
Kunawararak et al, 2011	30	30	29	30	1.2%	1.03 [0.94, 1.13]
Liu X. et al, 2015	913	966	945	1066	37.7%	1.07 [1.04, 1.09]
Mohammed S. et al, 2016	917	1104	903	1093	38.1%	1.01 [0.97, 1.04]
Sarah I. et al, 2013	17	18	17	19	0.7%	1.06 [0.87, 1.28]
Total (95% CI)		**2733**		**2947**	**100.0%**	**1.04 [1.02, 1.06]**
Total events	2390		2490			

Heterogeneity: Chi² = 7.54, df = 7 (P = 0.37); I² = 7%

Test for overall effect: Z = 3.71 (P = 0.0002)

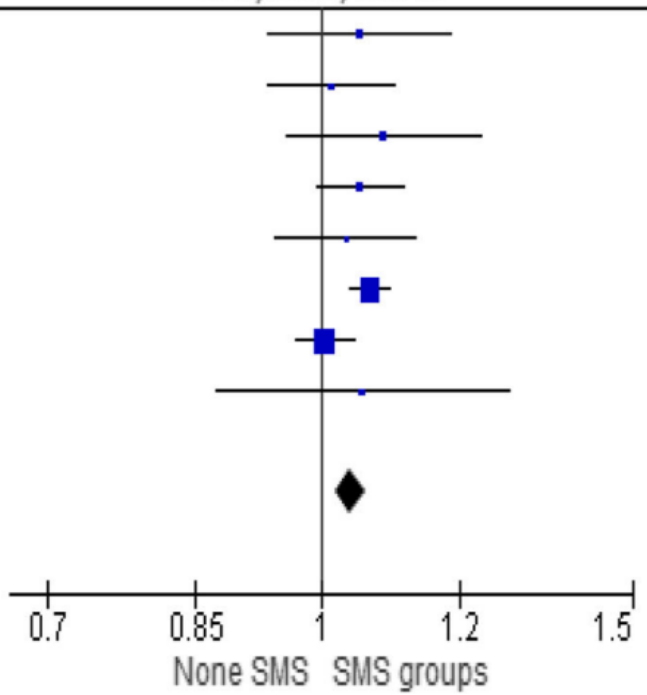


Fig. 3 Forest Plot of the effect of mobile-phone messaging on Anti-TB treatment success

Meta-analysis steps

- Identify comparisons to be made
- Identify outcomes to be reported and statistics to be used
- Enter data from each relevant study
- Combine the results to obtain a summary of effect
- Explore differences (heterogeneity) between the studies
- Explore sub-group analysis
- Interpret the results

Meta-analysis

- All methods essentially compute weighted averages
- Weighting factor is often the study size
- Statistical models for combining data:
  - Fixed effects model
    - assumes that the true effect of treatment is the same value in each study (fixed);
    - the differences between studies is solely due to random error
  - Random effects model
    - Assumes that the treatment effect varies within and between the individual studies around some overall average treatment effect
      - Allows for random error plus inter-study variability
      - Studies tend to be weighted more equally (relatively more weight is given to smaller studies)

Revman software for meta-analysis

- Revman software is free
- Cochrane's RevMan software free, downloadable at:

http://www.cc-ims.net/revman

Open science for Systematic Review process

Part 2

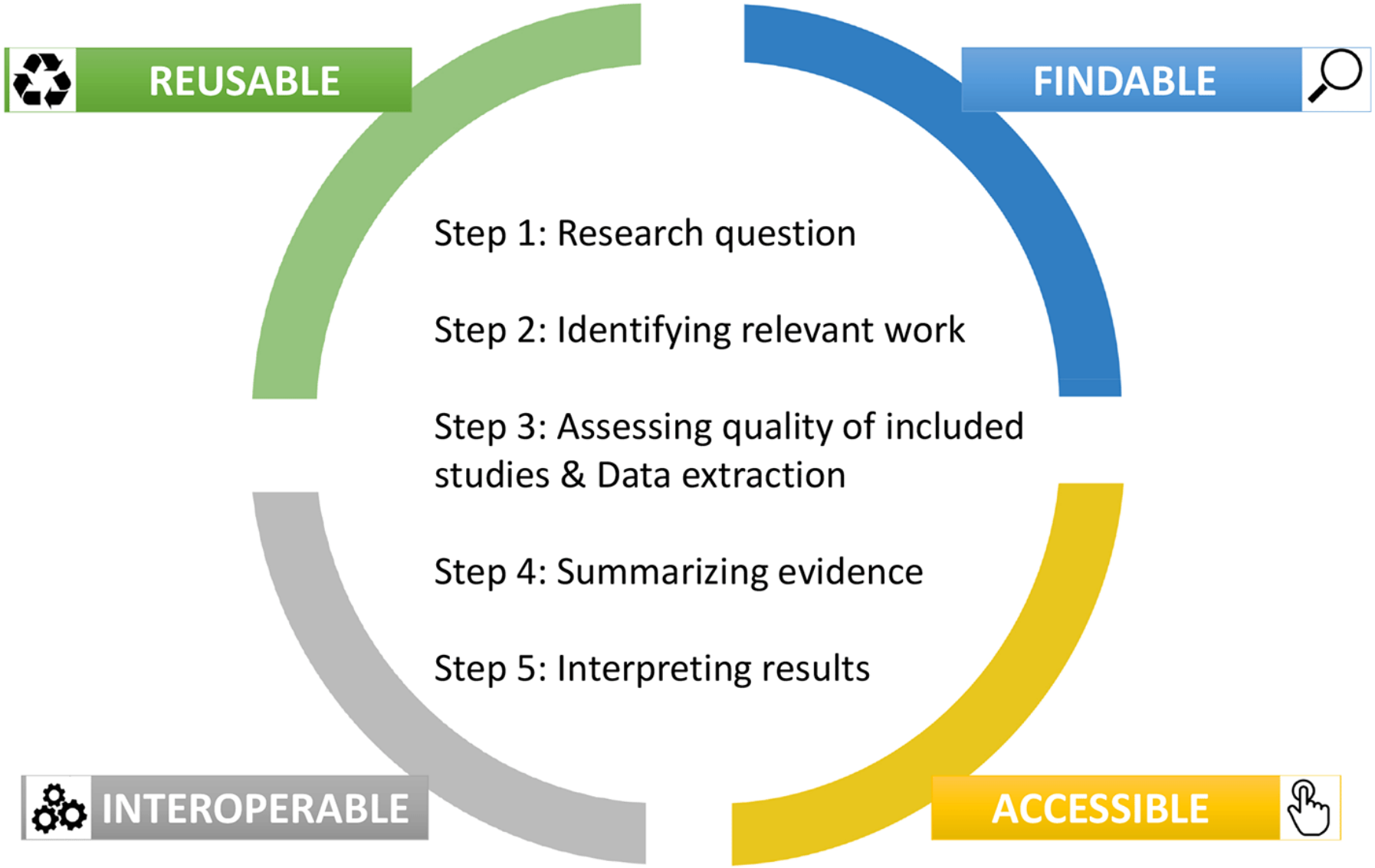
FAIR principles

- Good data management requires it to be:
- Findable
  - Assigned a globally unique persistent identifier
  - Data are registered
- Accessible
  - Data are retrievable
  - Protocol is open, free, and universally implementable
  - Protocol allows for an authentication and authorisation procedure
  - Metadata is accessible, even when data is no longer available
- Interoperable
  - use a formal, accessible, shared, broadly applicable language
  - Use vocabularies that follow FAIR principles
  - Include qualified references to other metadata
- Reusable
  - Richly described with accurate and relevant attributes
  - Released with a clear and accessible data usage license
  - Meet domain-relevant community standards

FAIR and systematic review process

- The SR process should be explicit and robust.
- FAIR principles require that data
  - should be registered in a searchable source and assigned a unique identifier
  - Should be retrievable (ideally through an automated procedure)
  - Available to be combined to maximise their value
  - Described in detail to facilitate reuse

Findability, Accessibility, Interoperability and Reusability in evidence synthesis.



Challenges in evidence synthesis and open research

Framing the review question

- An important step in evidence synthesis
- Researchers are challenged by limited access to ongoing or available systematic reviews addressing a similar topic

- Solution:
  - PROSPERO pre-registration
  - (International Prospective register of systematic reviews) since 2012
  - Open-access publication of papers
  - Pre-prints

Challenges in evidence synthesis and open research

Identifying relevant work

- A fundamental step in the SR process
- Developing a search strategy requires complex Boolean algorithms
- Bias can be introduced during screening of studies for eligibility

- Solution:
  - Publish search algorithms (in PROSPERO)
  - Ensures findable, accessible, reusable or modifiable
  - Avoids duplication
  - Screening done by at least two reviewers (with option for discrepancy resolution)

Challenges in evidence synthesis and open research

Data extraction and quality assessment

- Data collection from included studies
- Time consuming
- Making collected data available will reduce duplication
- Should assess risk of bias/methodologically validity

- Solution:
  - Data extraction and validity assessment to be done by at least two reviewers (with option for discrepancy resolution)
  - Use validated tools for risk of bias assessment
  - Pre-specify in PROSPERO

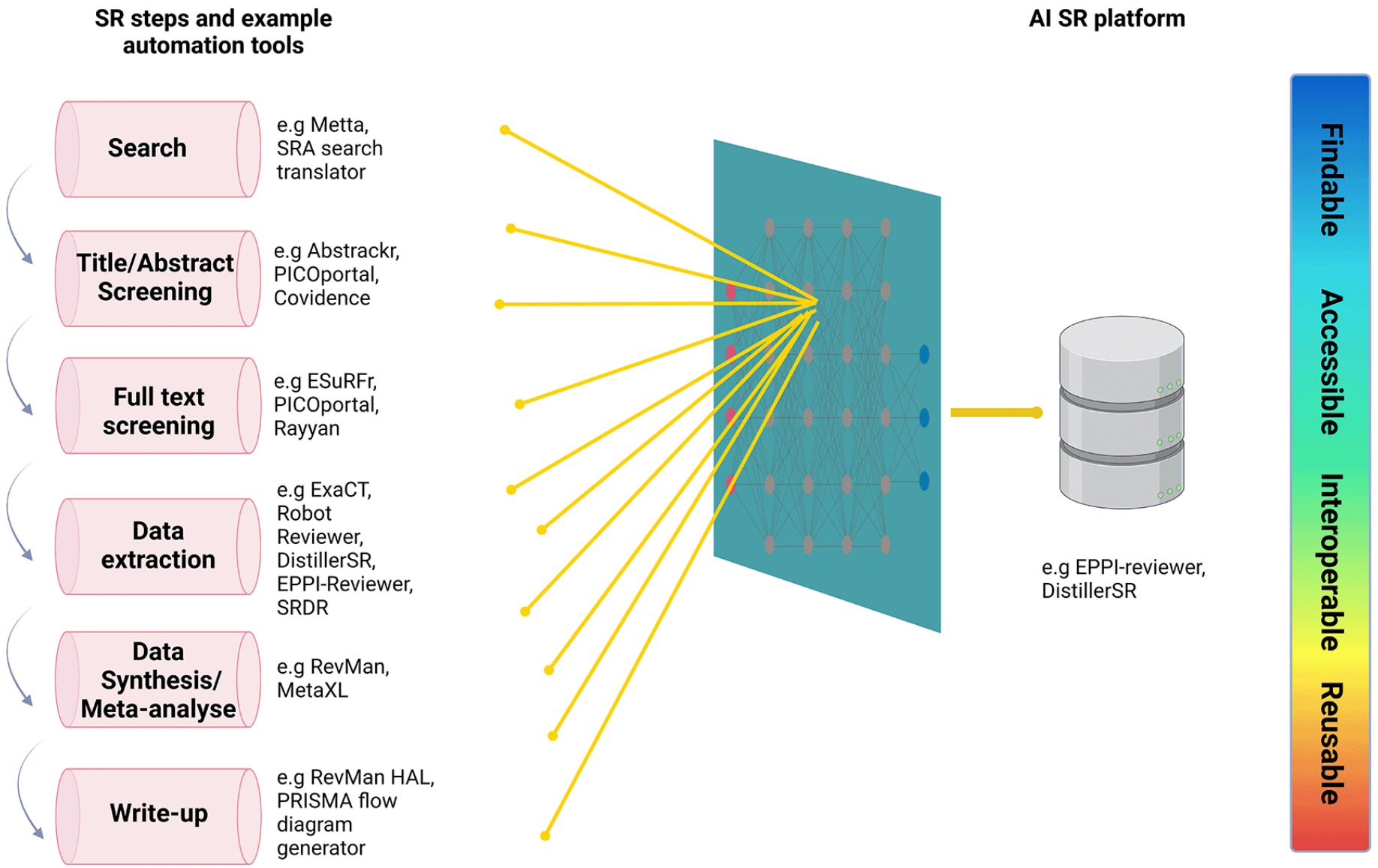
Barriers to implementing FAIR principles

- Several benefits in SR data sharing
- Challenges:
  - Ethical concerns
  - Ownership of data
  - Intellectual property rights
  - Recognition of data producers
- Solutions
  - Data repositories—acknowledge source of data
  - Creation of SR data repository
  - Journal policies

Potential role of AI in evidence synthesis

- Evidence synthesis is growing exponentially and consists of several routine, time-consuming steps
- Several AI methods and tools are already available to automate some of the steps
- AI includes:
  - machine learning (use computer algorithms)
  - natural language processing (analyse texts and extract vast information)

Automatable systematic review steps.



Conclusion

- Evidence synthesis requires transparency
- Implementing FAIR principles plays a crucial role in improving the reporting standards
- Already automation is helpful

Acknowledgements

This project was funded by the Berkeley Initiative for Transparency in the Social Sciences (BITSS), under the Center for Effective Global Action (CEGA).

- Already automation is helpful

Because science is cumulative, we must cumulate scientifically

Thank you