SYSTEMATIC REVIEWS AND META-ANALYSES

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Virtual Session 3 of 3

COURSE WEBSITE

- Slides and all other resources you'll need for the course are available at:

https://facenteconsulting.com/srmacourse/

CURRICULUM

Wednesday

- Overview of SRs and MAs
- PROSPERO and PRISMA
- Defining the review question
- PICOS

Thursday

- Searching for records and studies
- Screening records for inclusion

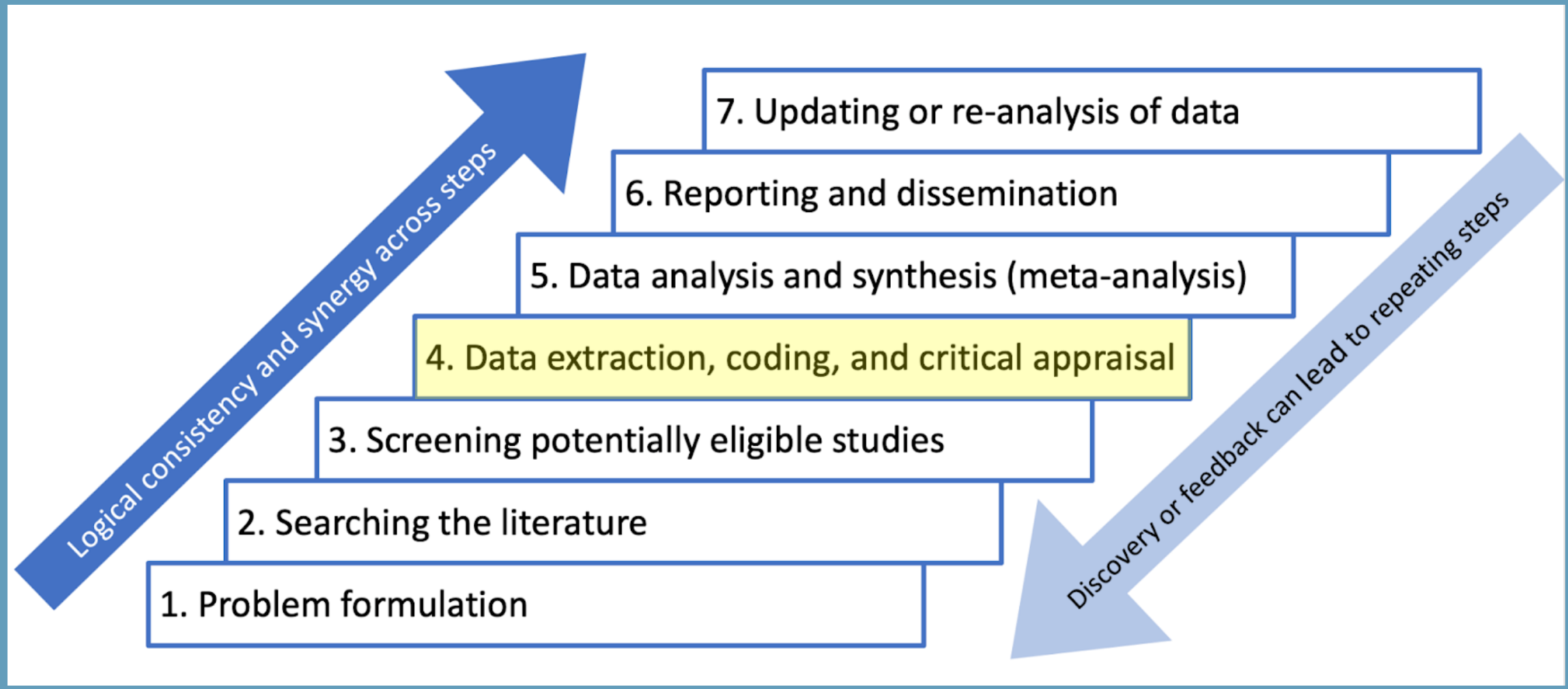
Friday

- Extracting and organizing data
- Summarizing data and meta-analysis
- Evaluating bias

In person, Week of Dec 1

- Review and practice defining the review question and PICOS criteria to be used
- Practice searching for records and screening returned studies
- Review of evaluating bias
  Practice extracting data
- Sensitivity analyses & stratified analyses
  Understanding SRMA limitations
  Interpreting and reporting results
- Reviewing special types of SRs and MAs
  Final chance for Q&A from the course

SYSTEMATIC REVIEWS PROCESS



https://oli.cmu.edu/courses/systematic-reviews-and-meta-analysis-o-f/#

HOW TO ACCESS FULL TEXT

Sometimes it can be very difficult to access articles behind a paywall. Options?

1. Look on Google Scholar, ResearchGate.net, and Academia.edu
2. Check https://osf.io
3. Try this tool: https://libguides.umflint.edu/openaccess
4. Try a request site, like subreddit r/scholar
5. Contact the author(s) and ask for a copy
6. See if there is a pre-print of the article (but note if this is what you use)

HOW TO ACCESS FULL TEXT

Dr Lisa Nivison-Smith
@LNivisonSmith

1. @SciHubUpdated

Online library created from downloading papers through institute logins to Scihub's own server.

✅Pros
- Claims to have 99% all papers

❌Cons
- questionable legality
- blocked in some countries
- no papers added since 2021

2:26 PM · Oct 5, 2022

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@LNivisonSmith

2. @unpaywall

A browser extension which finds paper PDFs legally by searching various online repositories

✅Pros
- Legal
- Extension automatically searches for paper in your browser

❌Cons
- Only on Firefox and chrome desktop browsers

2:26 PM · Oct 5, 2022

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@LNivisonSmith

3. Open Access Button

Similar to Unpaywall but if it canot find a PDF, the tool offers to email the authors to ask for the paper

✅Pros
- Legal
- More chance to find paper by asking authors

❌Cons
- Need to press button everytime to search for a paper

2:26 PM · Oct 5, 2022

Dr Lisa Nivison-Smith @LNivisonSmith · Oct 5, 2022

4. @PaperPandaHQ

A Chrome extension that finds the DOI of the paper from the current webpage, then searches for it from various repositories

✅Pros
- Can set search to include your institution's library

❌Cons
- Not clear if all databases searched are legal

2 23 301

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5. 12ftladder

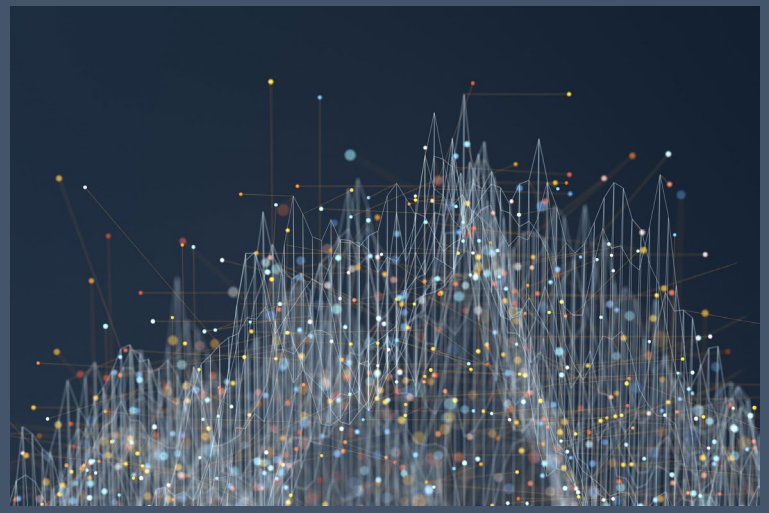
Finds the cached, unpaywalled version of a site seen by Google search

✅Pros
- No extension needed, just add 12ft.io before URL of a paywalled page

❌Cons
- Mostly for news sites
- Has been disabled for some sites

*Please note this is not a recommendation or endorsement to use any of these sites

EXTRACTING DATA



Develop a structured data extraction format

- List the specific information needed for the review (aligned with a priori plans described in the protocol)
- Decide how to handle data extraction, including organization, storage, and access
- Assign unique study identifiers (number or label)
- Assign report identifiers for each report linked to a study (and include reference to the relevant unique study ID)
  - For example, 01.02 refers to the second report in the first study
- Pilot test your format by testing if two separate coders extract the same data from the same study, and if not, attempt to resolve the discrepancies

Valentine, J. C., Pigott, T. D., & Hanratty, J. Unit 4: Screening potentially eligible studies. In J. C. Valentine, J. H. Littell, & S. Young (Eds.), *Systematic reviews and meta-analysis: A Campbell Collaboration online course*. Open Learning Initiative, 2023. Available from https://oli.cmu.edu/courses/systematic-reviews-and-meta-analysis/

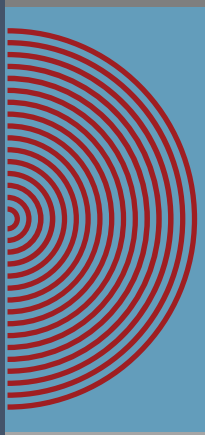
TYPES OF DATA TO EXTRACT

Full citation including:

- Author(s) in order of appearance
- Title
- Source
- Year of publication
- DOI, if available
- Type of publication
- Registry identifier, if available

Study design:

- Number of sites involved
- Types of sites
- Locations (countries)
- Types of locations (rural, urban, etc.)
- Number of groups/cohorts
- Comparison or control involved?
- How groups were formed
- Number/timing of waves



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TYPES OF DATA TO EXTRACT

Data collection:

- Name and source of measure (citations)
- Results of reliability and validity testing
- Are measures continuous or dichotomous?
- Are high scores negative or positive events?
- Timing of assessments
- Data sources (self-reported, caregiver, administrative records, etc.)

Methods for data collection:

- Who collected data? (researchers, providers, self-reported, etc.)
- Double-blinded? (Were the researchers blinded to group status?)
- How were data collected? (phone call, surveys, in-person meetings, etc.)

Valentine, J. C., Pigott, T. D., & Hanratty, J. Unit 4: Screening potentially eligible studies. In J. C. Valentine, J. H. Littell, & S. Young (Eds.), *Systematic reviews and meta-analysis: A Campbell Collaboration online course*. Open Learning Initiative, 2023. Available from https://oli.cmu.edu/courses/systematic-reviews-and-meta-analysis/

TYPES OF DATA TO EXTRACT

Participants:

- Demographic data
  - Age (range, mean, sd)
  - Gender (#/%)
  - Region/country
  - Socioeconomic status
  - Other relevant status
- Health status
- Mental health status

Sample size/composition:

- Number potentially eligible
- Confirmed eligible
- Included in the study
- Completed follow-up
- Included in reporting

Valentine, J. C., Pigott, T. D., & Hanratty, J. Unit 4: Screening potentially eligible studies. In J. C. Valentine, J. H. Littell, & S. Young (Eds.), *Systematic reviews and meta-analysis: A Campbell Collaboration online course*. Open Learning Initiative, 2023. Available from https://oli.cmu.edu/courses/systematic-reviews-and-meta-analysis/

TYPES OF DATA TO EXTRACT

Intervention information:

- Duration (in weeks, months; minimum, maximum, mean, sd)
- Hours of direct contact
- Frequency of contact
- Collateral contacts
- Types of services
- Service provider characteristics

Study results (especially required for MA):

- Effect size calculations
- Association or difference in proportions or means
- Variance
- Number (n) for each group, for each measure, for each data point

Valentine, J. C., Pigott, T. D., & Hanratty, J. Unit 4: Screening potentially eligible studies. In J. C. Valentine, J. H. Littell, & S. Young (Eds.), *Systematic reviews and meta-analysis: A Campbell Collaboration online course*. Open Learning Initiative, 2023. Available from https://oli.cmu.edu/courses/systematic-reviews-and-meta-analysis/

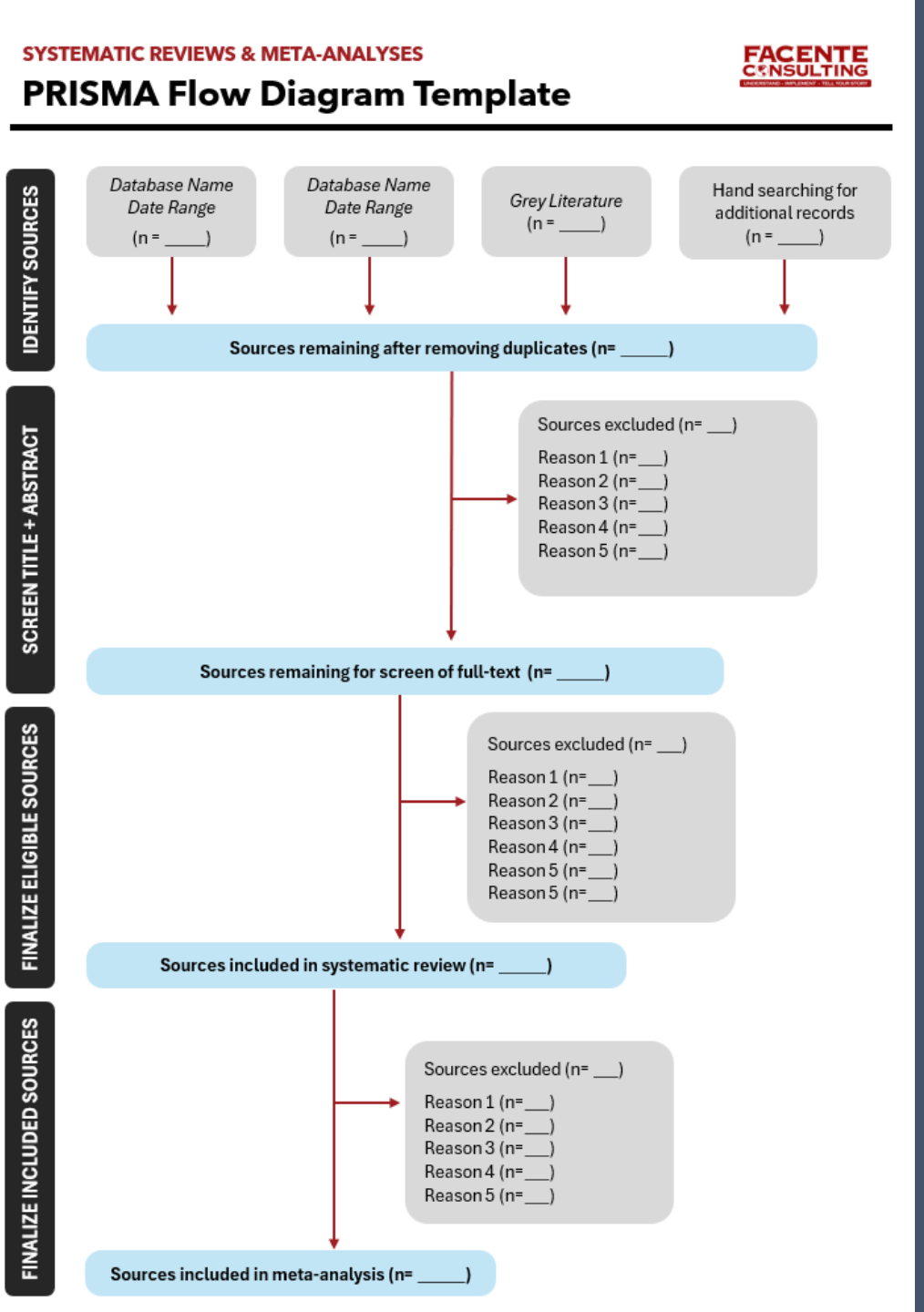
DEVELOPING FIGURE 1

Template is provided by PRISMA 2020

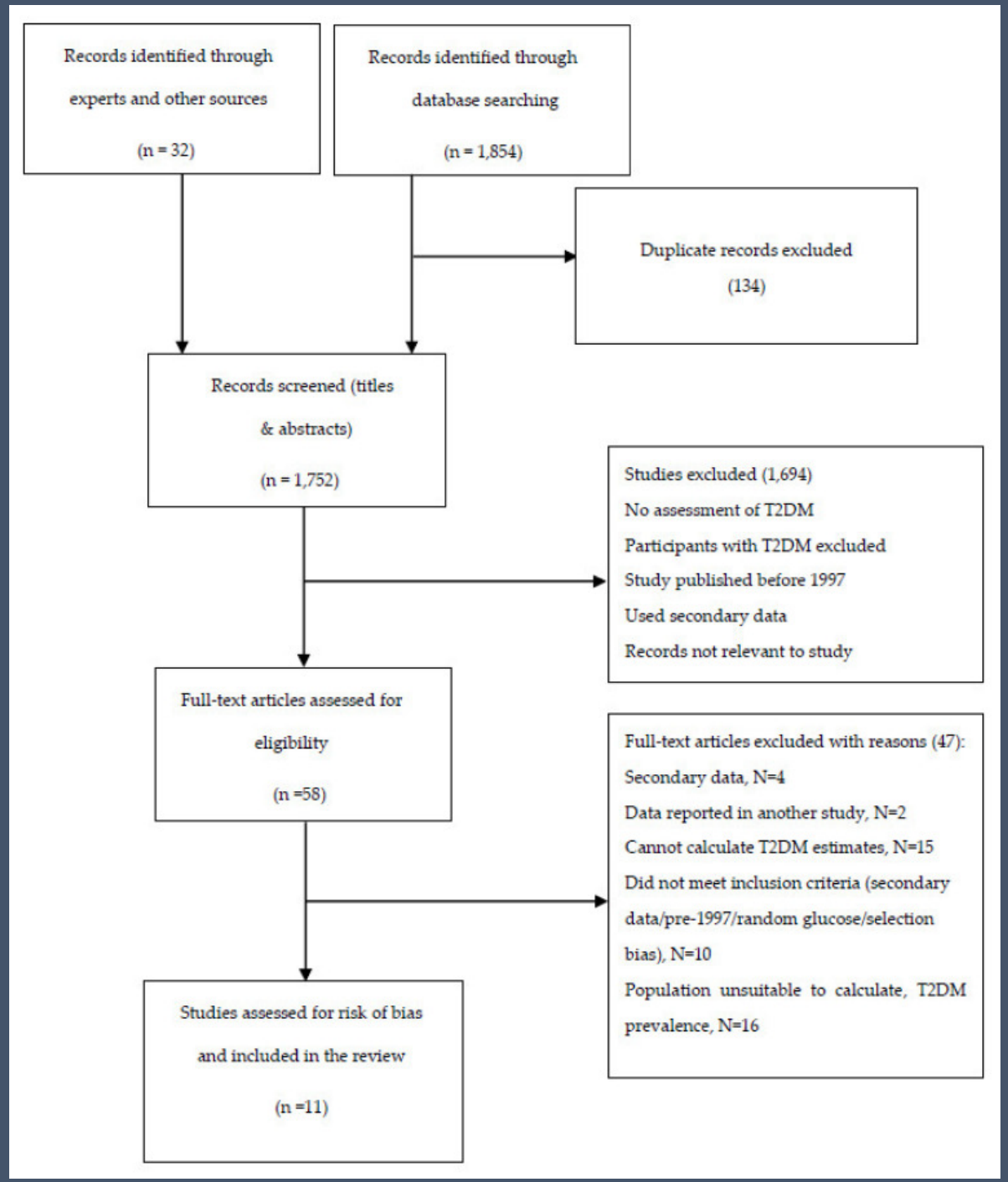
https://www.prisma-statement.org/prisma-2020-flow-diagram

(and a modified template is provided for this course, on the course website)

We will review each section and discuss

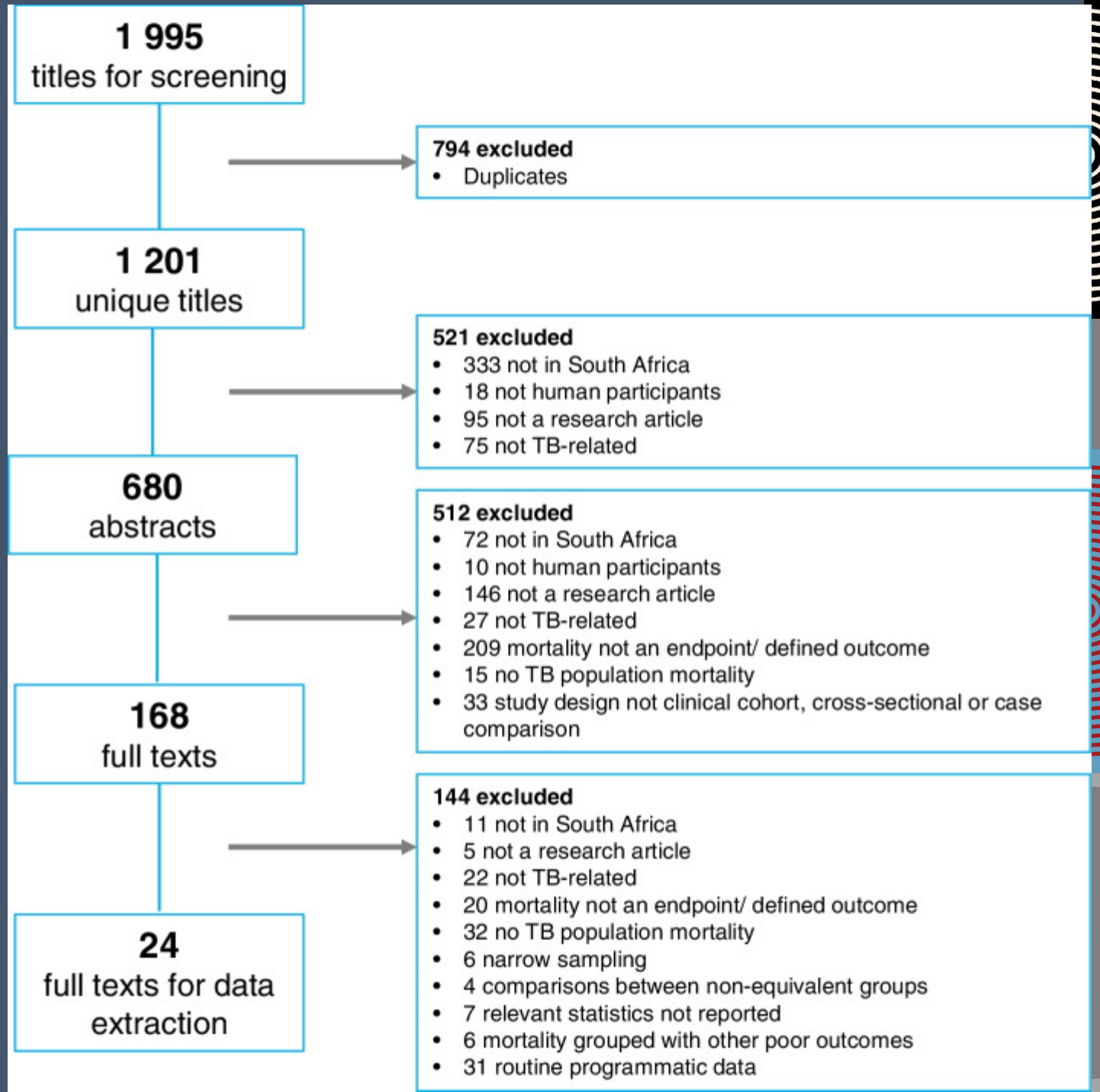


SCREENING RECORDS



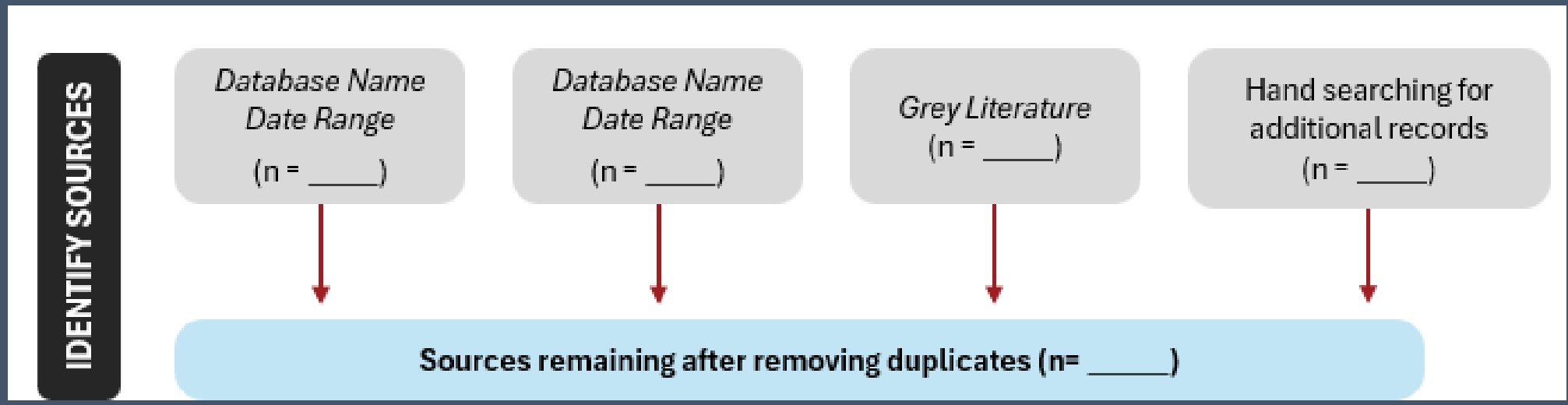
https://pubmed.ncbi.nlm.nih.gov/34070714/

SCREENING RECORDS



https://pubmed.ncbi.nlm.nih.gov/36814335/

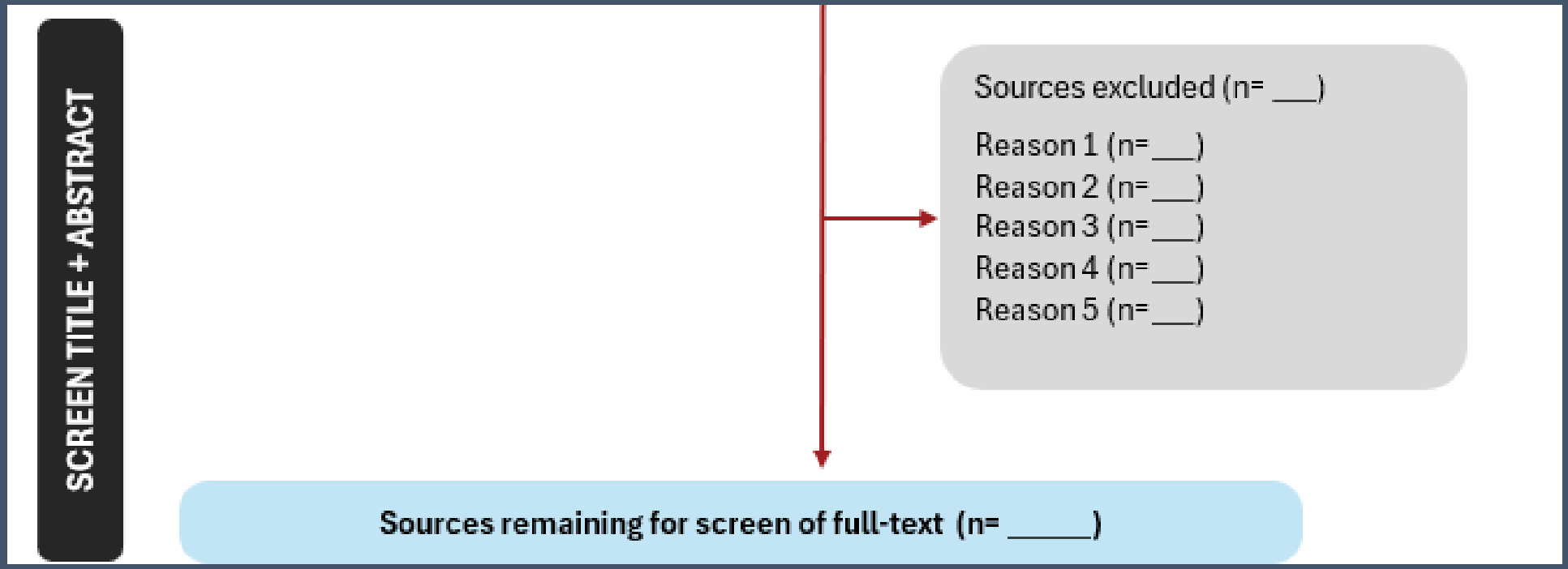
DEVELOPING FIGURE 1: IDENTIFICATION



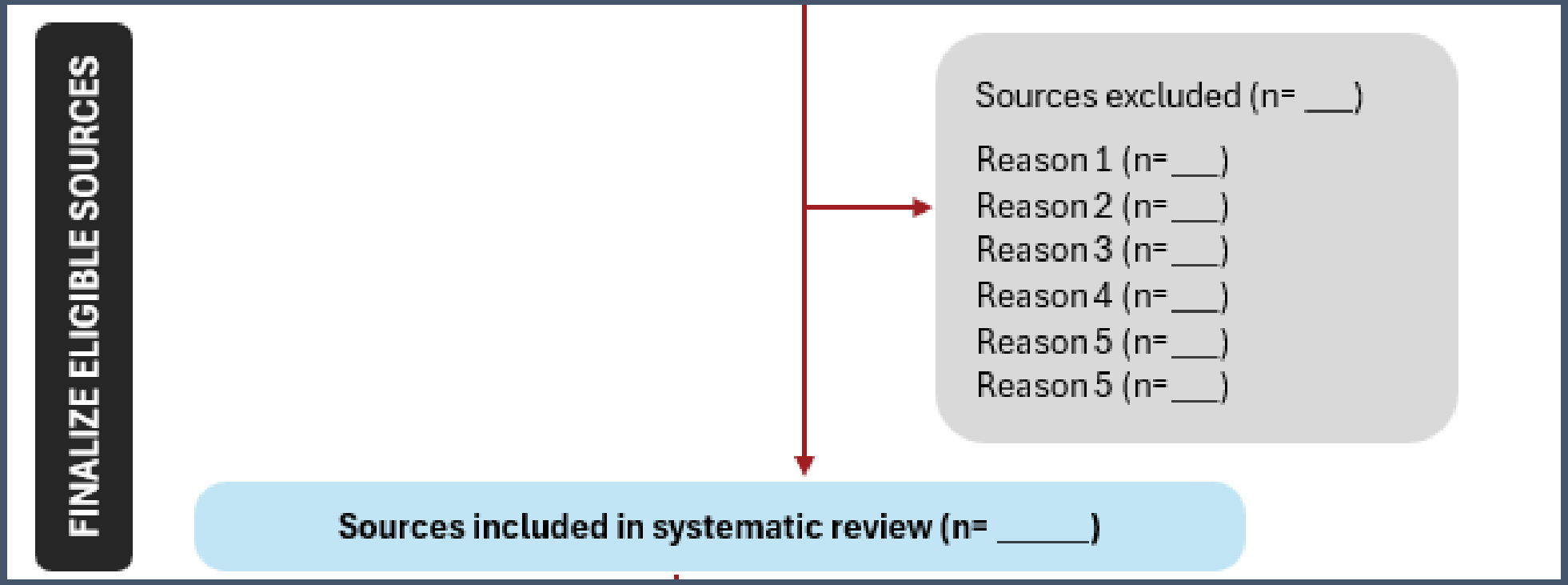
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

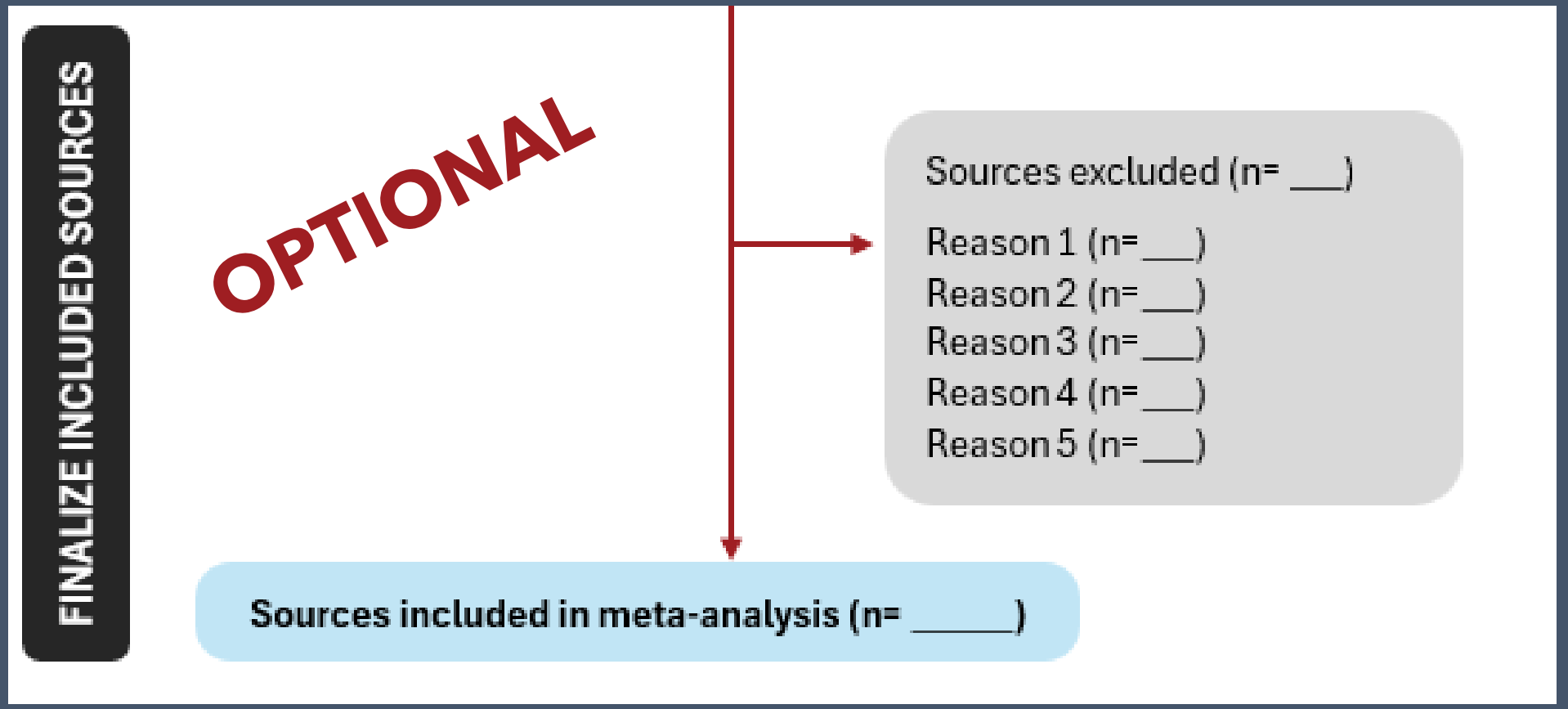
DEVELOPING FIGURE 1: SCREENING



DEVELOPING FIGURE 1: INCLUDED



DEVELOPING FIGURE 1: META-ANALYZED (IF APPLICABLE)



EXAMPLES OF FIGURE 1

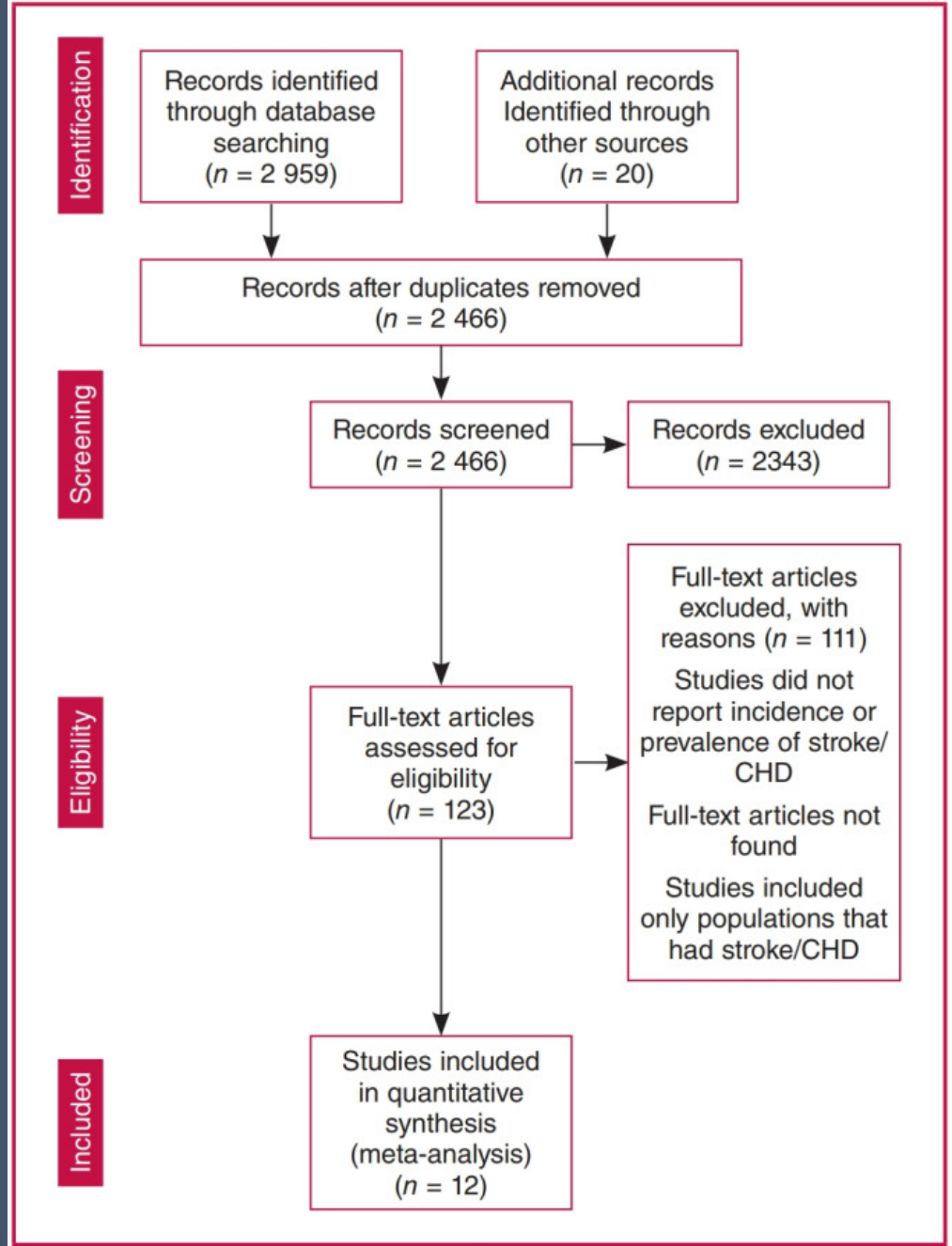
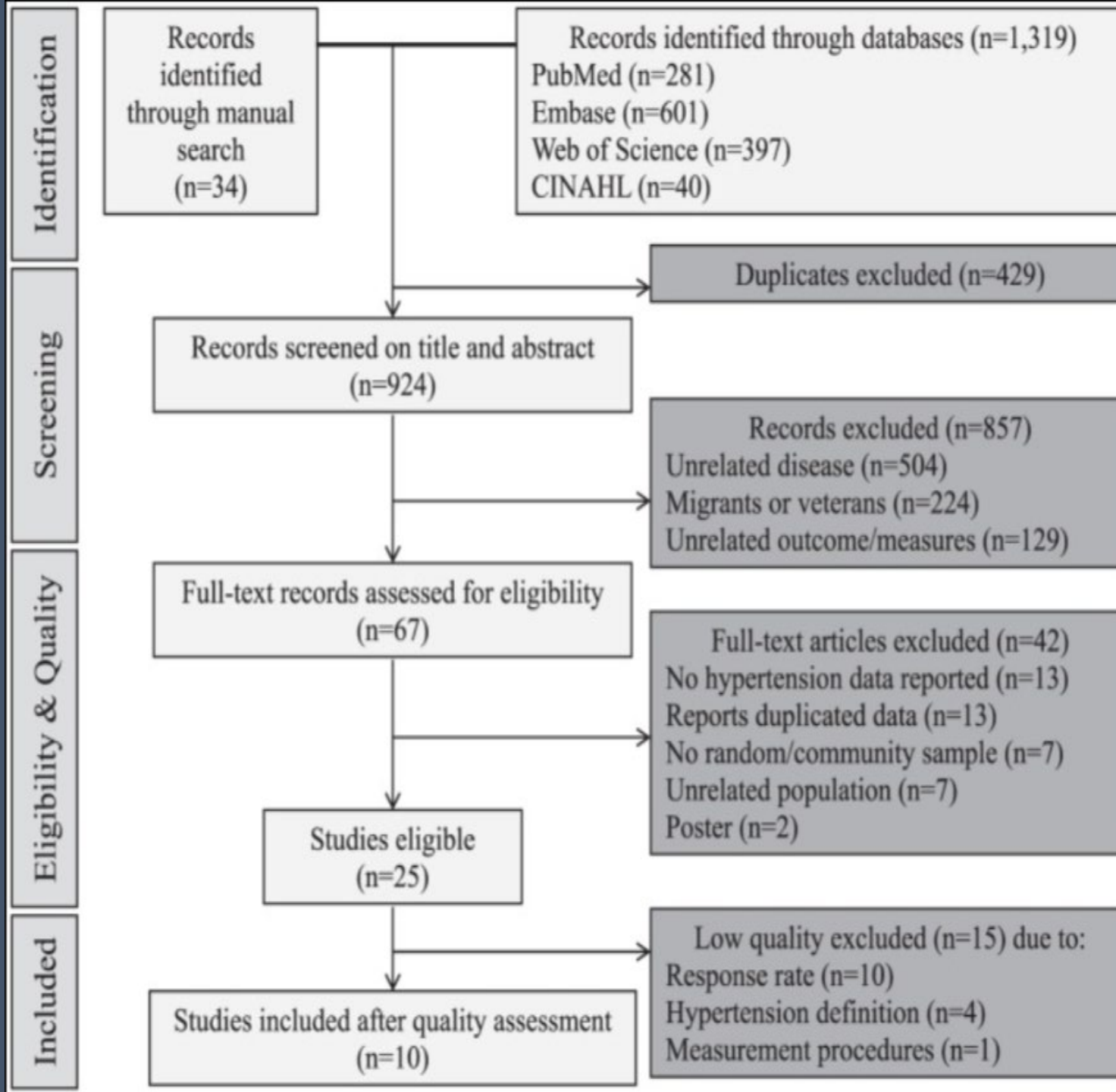


Fig. 1. Study-selection process using the PRISMA flow diagram.

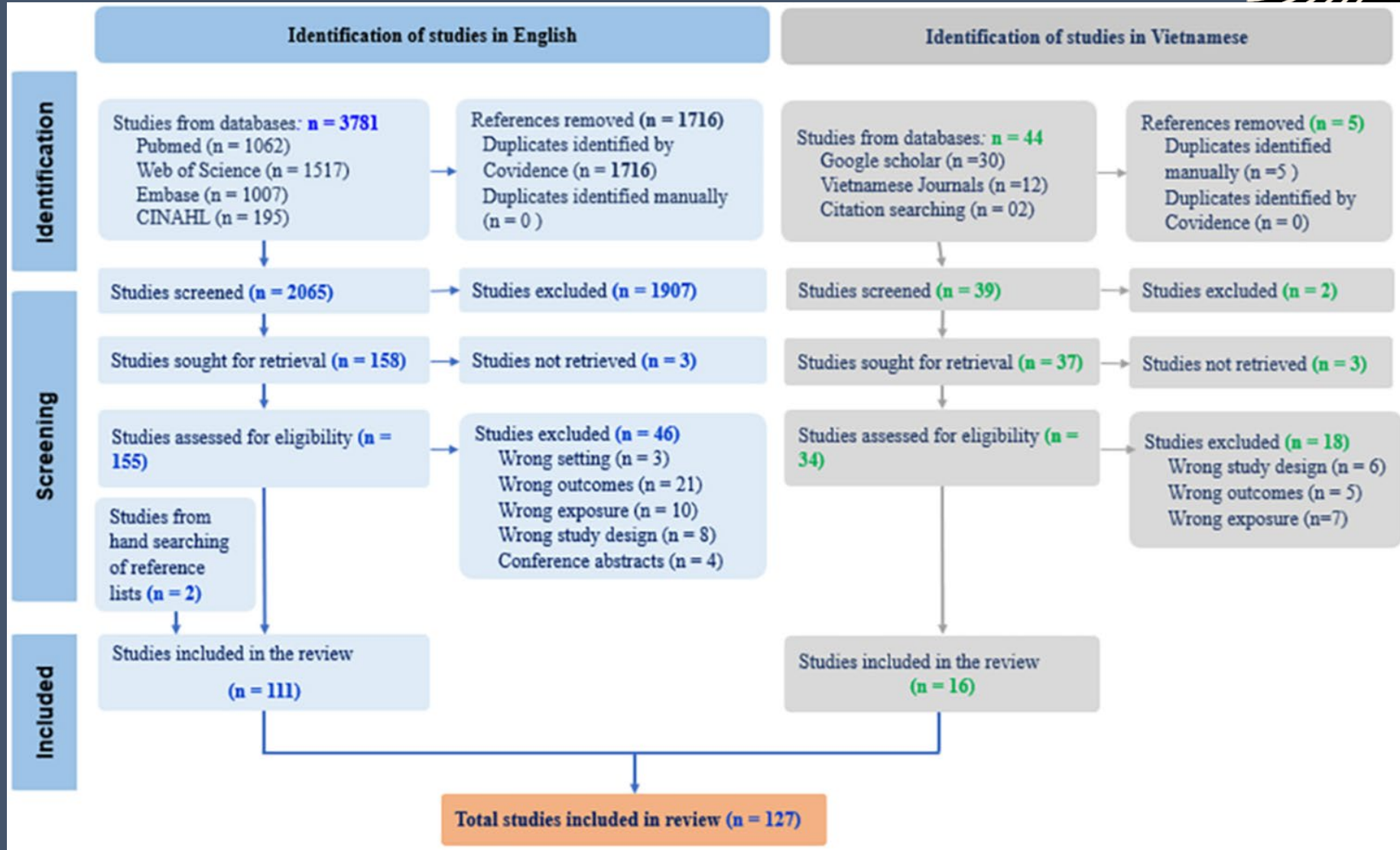
Abdelatif N, Peer N, Manda SO. National prevalence of coronary heart disease and stroke in South Africa from 1990-2017: a systematic review and meta-analysis. Cardiovasc J Afr. 2021 May-Jun 23;32(3):156-160. doi: 10.5830/CVJA-2020-045. Epub 2021 Mar 26. PMID: 33769427; PMCID: PMC8756070.

EXAMPLES OF FIGURE 1



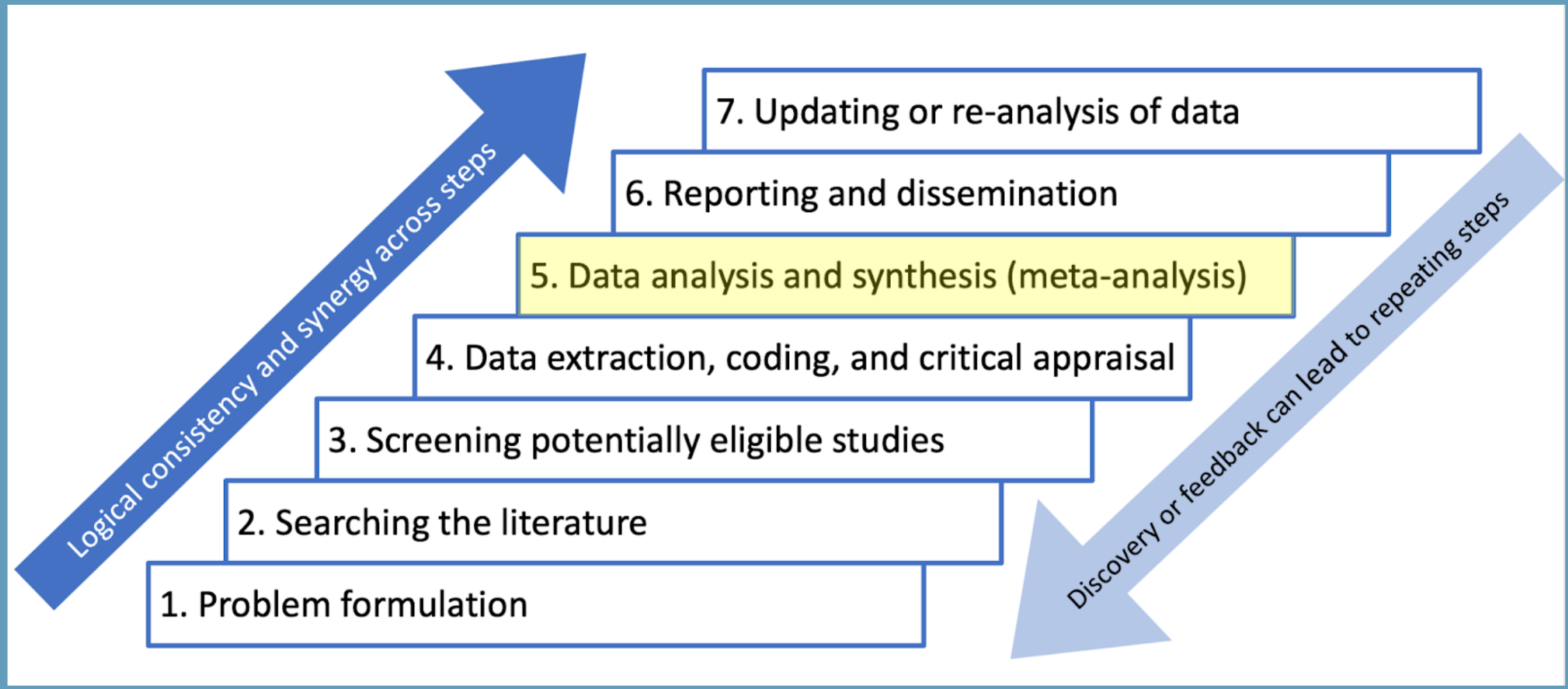
Meiqari L, Essink D, Wright P, Scheele F. Prevalence of Hypertension in Vietnam: A Systematic Review and Meta-Analysis. Asia Pac J Public Health. 2019 Mar;31(2):101-112. doi: 10.1177/1010539518824810. Epub 2019 Jan 24. PMID: 30678477; PMCID: PMC6463272.

EXAMPLES OF FIGURE 1



Linh Tran NQ, Cam Hong Le HT, Pham CT, Nguyen XH, Tran ND, Thi Tran TH, Nghiem S, Ly Luong TM, Bui V, Nguyen-Huy T, Doan VQ, Dang KA, Thuong Do TH, Thi Ngo HK, Nguyen TV, Nguyen NH, Do MC, Ton TN, Thu Dang TA, Nguyen K, Tran XB, Thai P, Phung D. Climate change and human health in Vietnam: a systematic review and additional analyses on current impacts, future risk, and adaptation. Lancet Reg Health West Pac. 2023 Nov 15;40:100943. doi: 10.1016/j.lanwpc.2023.100943. PMID: 38116497; PMCID: PMC10730327.

SYSTEMATIC REVIEWS PROCESS



https://oli.cmu.edu/courses/systematic-reviews-and-meta-analysis-o-f/#

META-ANALYSIS IS A TWO-STEP PROCESS

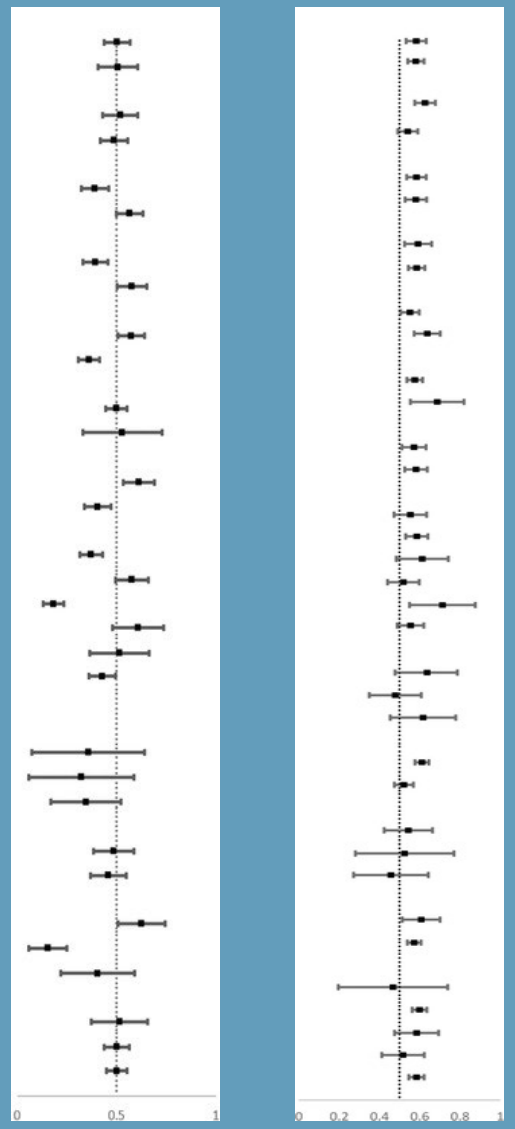
1. Calculate a summary statistic for each study to be included
    - This ensures having an equivalent measure to describe the observed effect across studies
2. Calculate a weighted average of the intervention effects estimated in individual studies to arrive at a combined summary statistic

$$\text{weighted average} = \frac{\text{sum of(estimate} \times \text{weight)}}{\text{sum of weights}} = \frac{\sum Y_i W_i}{\sum W_i}$$

https://training.cochrane.org/handbook/current/chapter-10

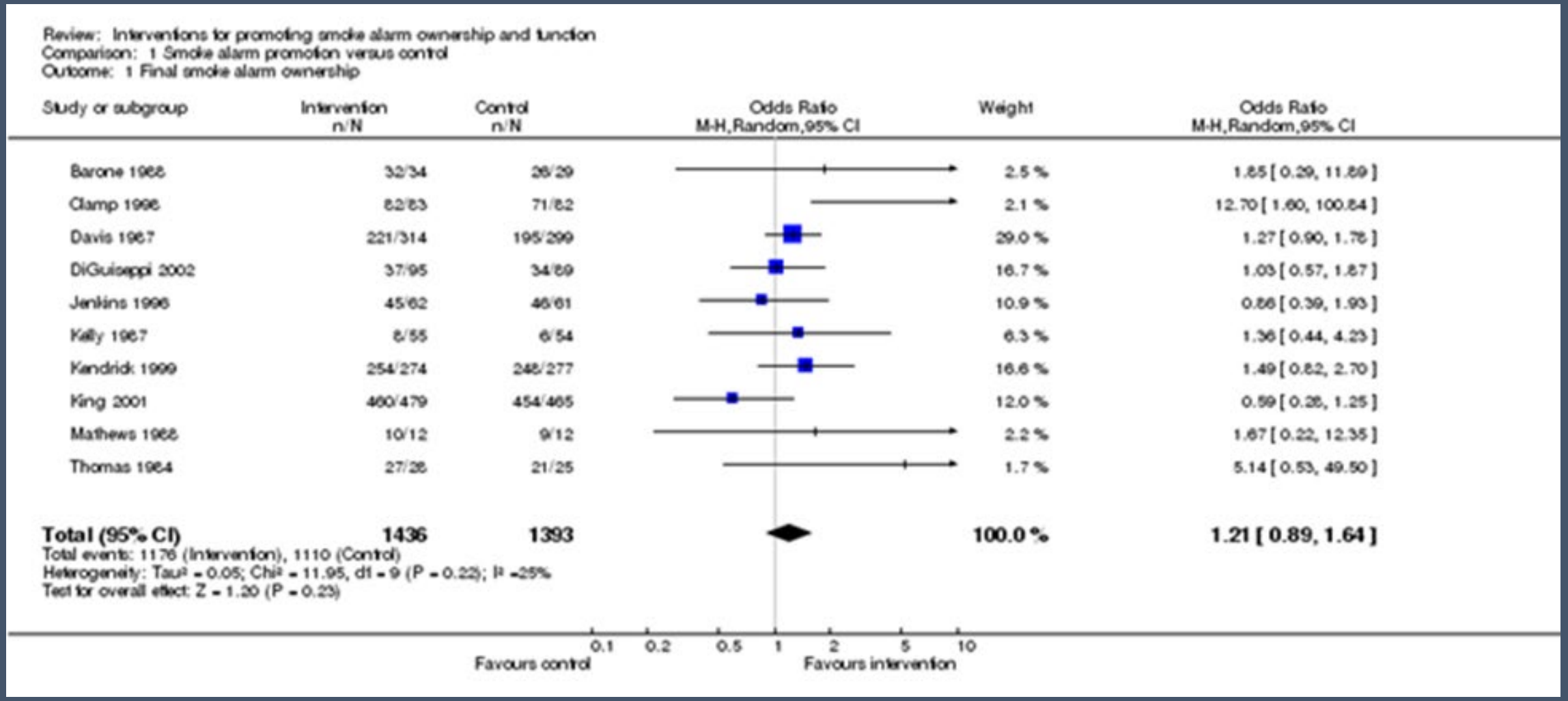
MA FOREST PLOT

- A meta-analysis is typically illustrated through the use of a forest plot
- A forest plot displays effect estimates and confidence intervals for both individual studies and the meta-analysis



https://training.cochrane.org/handbook/current/chapter-10
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8901150/

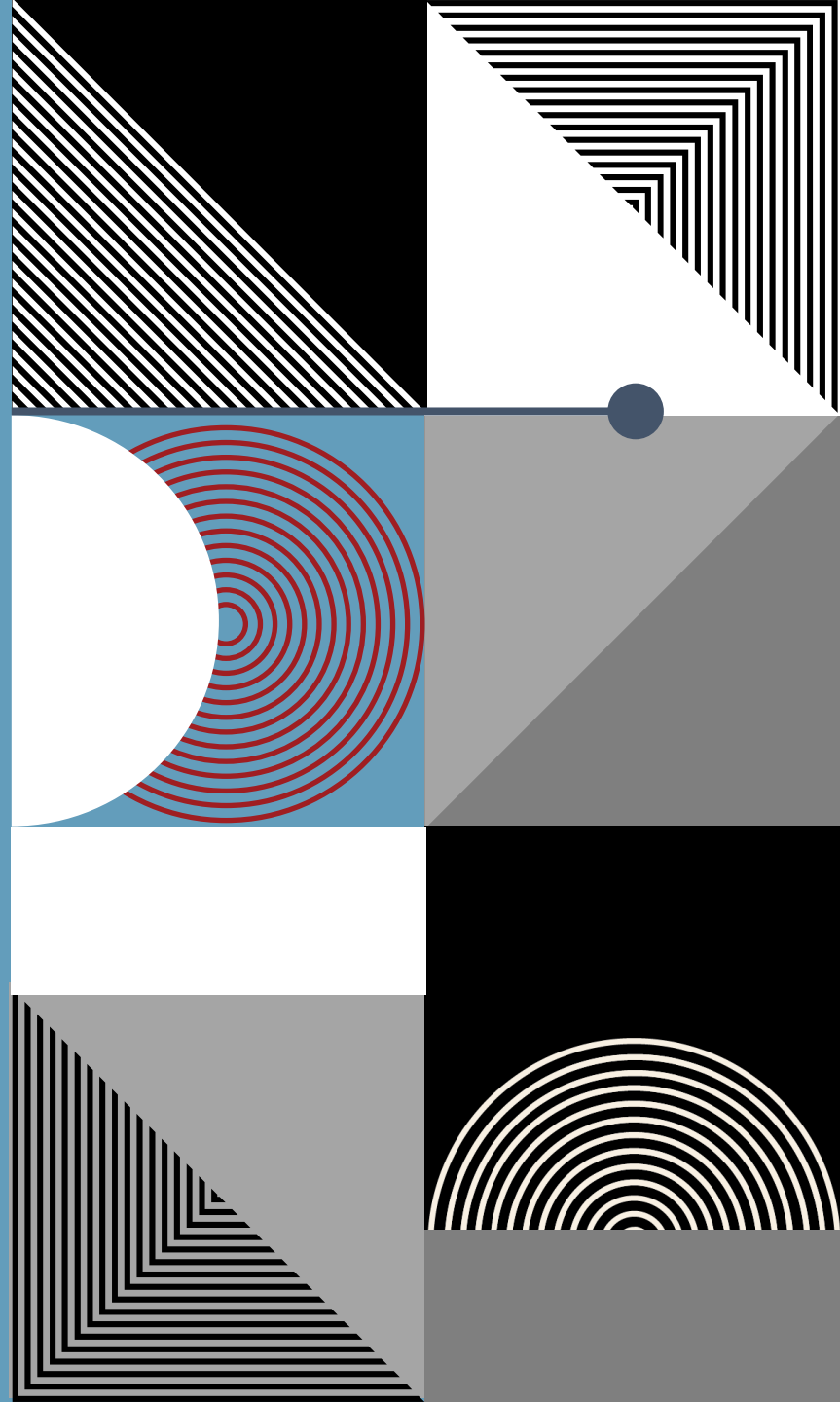
FOREST PLOT



https://training.cochrane.org/handbook/current/chapter-10

CREATING A FOREST PLOT

- Can be developed in statistical software
- How to do without stats software
  - https://www.youtube.com/watch?v=gD9r3tAZK60



CALCULATING COMBINED EFFECTS

Random effects: Assumes different studies are estimating different yet related intervention effects.

Fixed effects: Assumes that all studies are estimating the same intervention effects with their effects estimates.

Weights

- Often (but not always) use inverse variance
  - Larger studies have smaller standard error / given higher weight

https://training.cochrane.org/handbook/current/chapter-10

PRIMARY ISSUES WITH MA

- What to do about heterogeneity
  - Clinical diversity
  - Methodological diversity
  - Statistical heterogeneity
  - Some or all of these

- Missing data may introduce bias
  - Missing outcomes (selective reporting bias)
  - Missing individuals (selection bias)
  - Missing studies (publication bias)
  - More…

https://training.cochrane.org/handbook/current/chapter-10

AVOIDING COMMON MA PITFALLS

1. Ensure all studies are the same study type
2. Be aware of publication bias, which will affect your findings (more tomorrow)
3. Be aware of missing data from individual studies
4. MA based on means are only appropriate for data that are ~normally distributed
    - Check whether data are skewed
    - Transform data if needed
    - Don’t mix log-transformed and untransformed data
5. Are you comparing apples and oranges? Or apples and…chickens?

https://training.cochrane.org/handbook/current/chapter-10

Evaluating Risk of Bias

Bias is a “systematic error or deviation from the truth” and can stem from a variety of issues, including reporting bias, evidence selection bias, or publication bias.

Within systematic review, bias can be introduced from individual studies or the portfolio of studies included

Bias is not always an indicator of poor study quality, in fact bias can be introduced in well-conducted studies.

EVALUATING RISK OF BIAS

Risk of Bias assessment (AKA quality assessment, critical appraisal)

RoB 2 Tool for randomized trials

www.riskofbias.info

Box 2. The RoB 2 tool (part 1): Preliminary considerations

Study design

- ☐ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

: Experimental: | Comparator:

Specify which outcome is being assessed for risk of bias

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result…?

ROB 2 – 5 DOMAINS

"(1) bias arising from the randomization process;

(2) bias due to deviations from intended interventions;

(3) bias due to missing outcome data;

(4) bias in measurement of the outcome;

(5) bias in selection of the reported result."

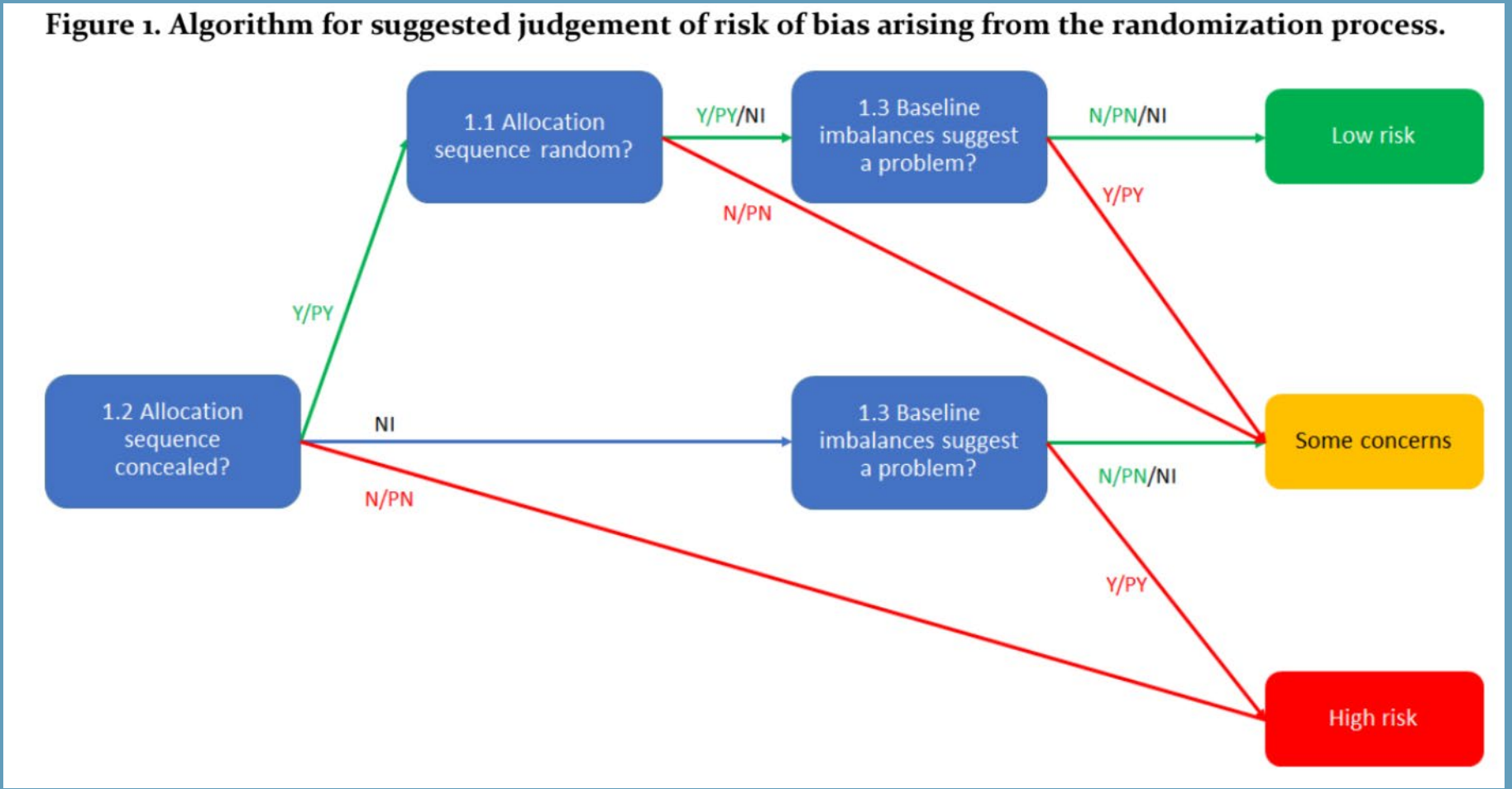
https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2

Box 4. The RoB 2 tool (part 2): 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
1.3 Did baseline differences between	*Note that differences that are compatible with chance do not lead to a risk of bias. A small number of differences identified as 'statistically significant' at the conventional 0.05 threshold should usually be considered to be compatible with chance.*	Y/PY/PN/N/NI

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

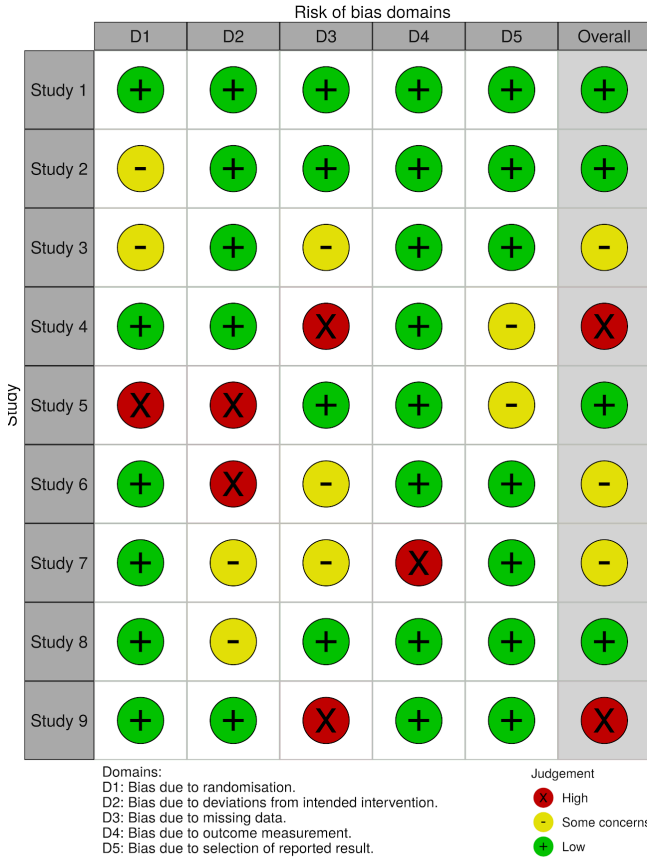
EVALUATING RISK OF BIAS

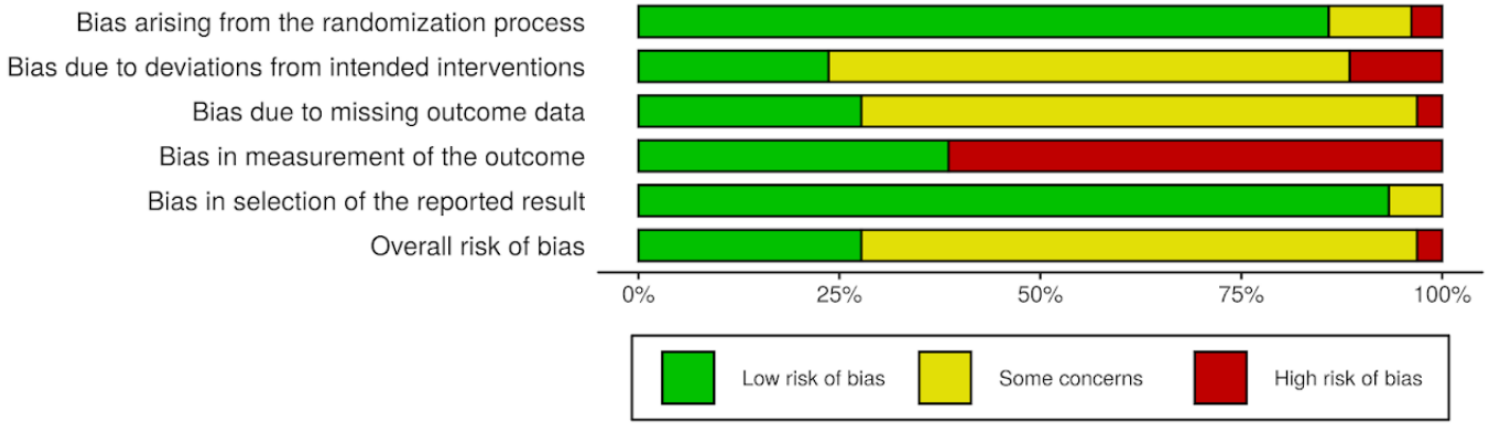


1. Low risk
2. Some concerns
3. High risk

https://drive.google.com/file/d/19R9savfPdCHC8XLz2iiMvL_71lPJERWK/view

- **Robvis tool for displaying assessments of risk for bias**
- **Tool creates publication quality traffic light plots and weighted bar plots**





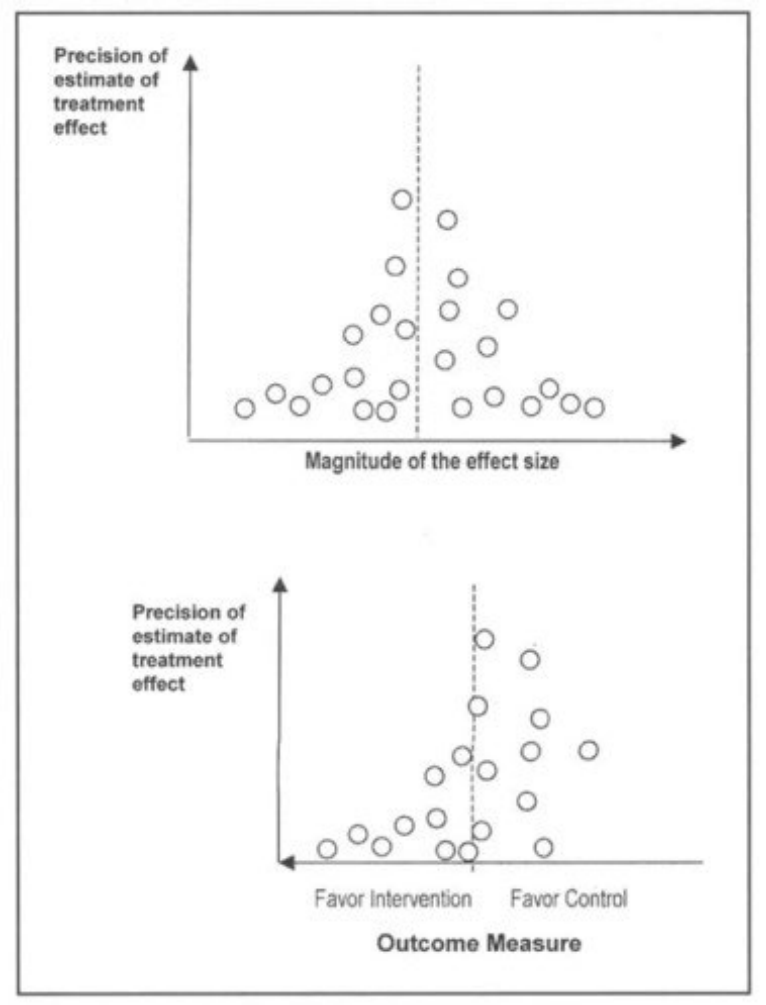
EVALUATING PUBLICATION BIAS

One key factor that may affect the conclusions reached by many such reviews is the hidden elephant of publication bias. In this issue of *Anesthesia & Analgesia*, Hedin et al[1] provide an assessment of the extent to which systematic reviews and meta-analyses reported in major anesthesia journals include evaluations of publication bias. Describing publication bias as the tendency to publish "only results that are statistically or clinically significant," they found that, among 207 systematic reviews meeting inclusion criteria, only 114 (55%) discussed it and 89 (43%) evaluated it. Furthermore, they found that only 68 (33%) of the reviews reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (a number that may be artificially low as an estimate of the proportion following reporting guidelines in these studies, given that guidelines other than PRISMA were predominant before 2009), which clearly recommend the assessment of publication bias as a means for avoiding situations in which "[t]he absence of information from some studies may pose a serious threat to the validity of a review."[2]

- Publication bias is also known as non-reporting bias.
- Can lead to overestimation of the true effect size

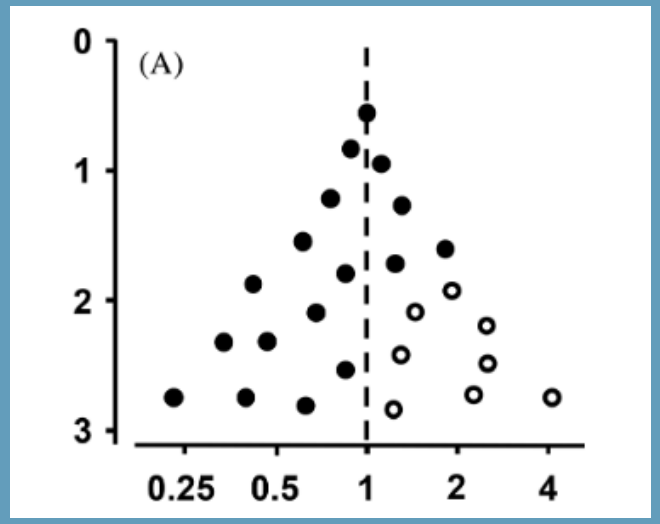
Dalton JE, Bolen SD, Mascha EJ. Publication Bias: The Elephant in the Review. *Anesth Analg*. 2016;123(4):812-813. doi:10.1213/ANE.0000000000001596

EVALUATING PUBLICATION BIAS

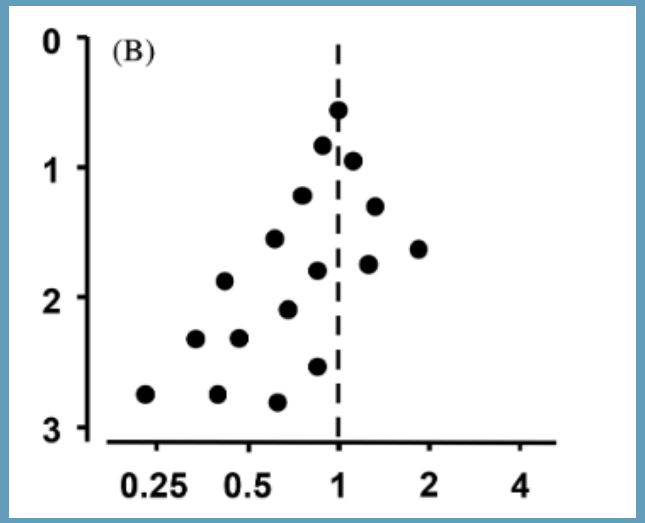


Funnel plot asymmetry

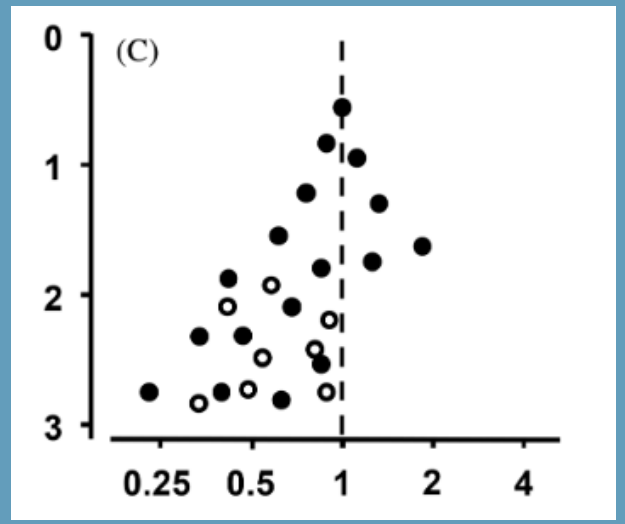
EVALUATING PUBLICATION BIAS



Symmetrical plot in the absence of reporting bias (open circles indicate smaller studies showing no statistically significant results)



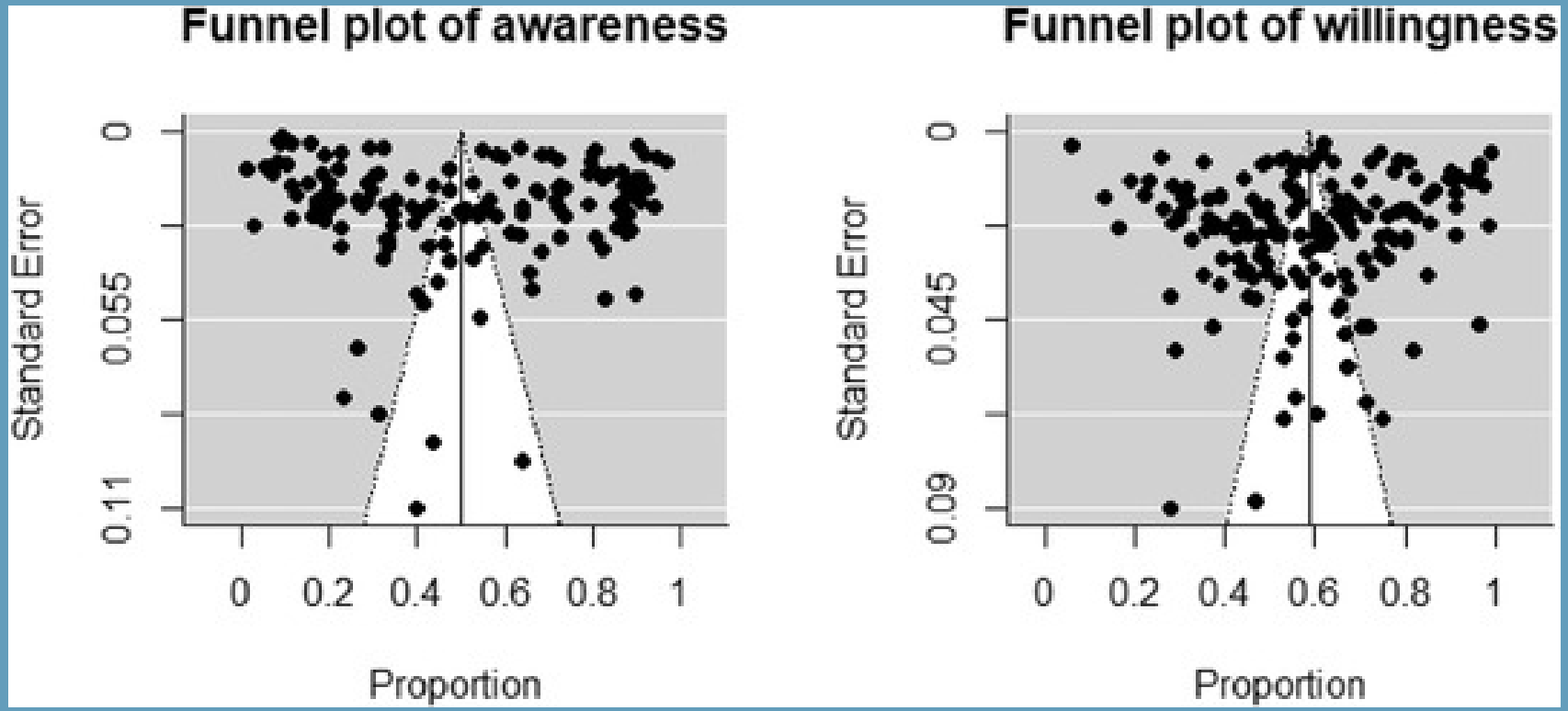
Asymmetrical plot in the presence of reporting bias (smaller studies showing no statistically significant results are missing)



Asymmetrical plot in the presence of bias due to methodologically flawed smaller studies (open circles indicate small studies using few methodological safeguards, whose results are biased toward larger effects)

Page, Sterne, Higgins, and Egger. Investigating and dealing with publication bias and other reporting biases in meta-analyses of health research: A review. Res Synth Methods. 2021 Mar; 12(2):248-259.

PUBLICATION BIAS FUNNEL PLOTS



SR on PrEP awareness and willingness