

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

AHRQ

Quantitative Synthesis

Chapter 1. Decision to combine trials

Prepared for:
The Agency for Healthcare Research and Quality (AHRQ)
Training Modules for Systematic Reviews Methods Guide
www.ahrq.gov

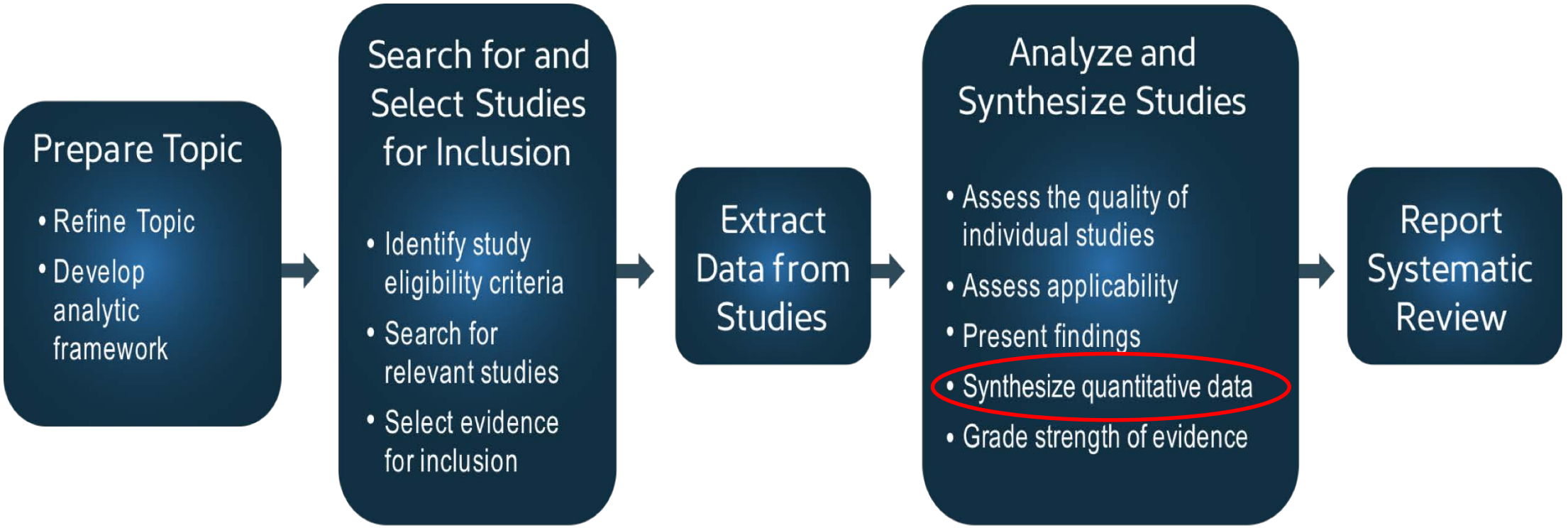
Background

- Purpose:
  - To consolidate and update guidance from prior methods guides
  - Focuses on ***Comparative Effectiveness Reviews (CERs):***
    - Systematic reviews comparing effectiveness and harms of alternative clinical options
    - Help clinicians, policy-makers, patients make informed treatment choices
  - Focuses on interventional studies, not diagnostic, individual-level, or observational studies

Background

- Quantitative synthesis (meta-analysis) is a critical component of comparative effectiveness reviews (CERs).
- Quantitative synthesis should be conducted transparently, consistently, with methodology explicitly reported.
- This guide supports this process, but is not a comprehensive review or a text.
- Addresses the issues commonly encountered conducting CERs, in the order they occur.

Systematic review process overview



Learning objective for Chapter 1. Decision to combine trials

- Learning objective: Describe the basic principles of combining data and when this is appropriate.

Decision to combine trials

- The first fundamental question in quantitative synthesis is, “Is it appropriate to pool the results of the identified studies?”[2]
- Many factors must be considered when deciding whether to combine studies in meta-analysis:
  - Clinical factors
  - Methodological factors
  - Statistical factors
- Studies must be reasonably similar to be pooled in meta-analysis.[1]

1. Verbeek J, Ruotsalainen J, Hoving JL. Synthesizing study results in a systematic review. Scand J Work Environ Health. 2012;38(3):282-90. http://dx.doi.org/10.5271/sjweh.3201

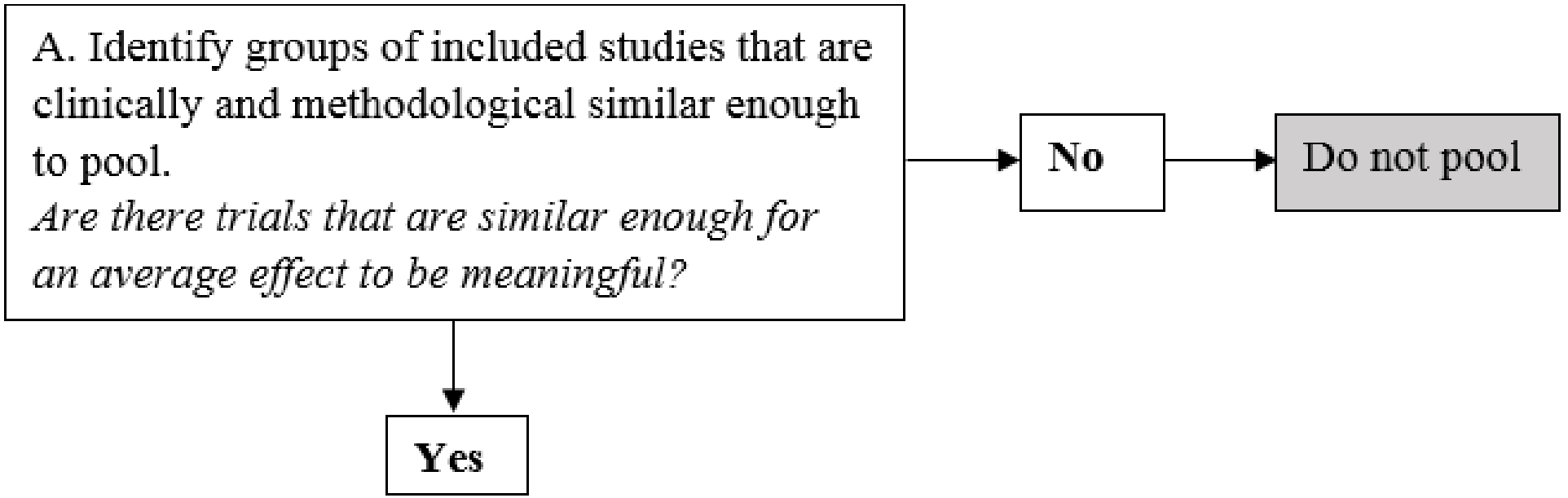
Decision to combine trials

- Assessing whether studies are reasonably similar requires considering heterogeneity.
- ***Clinical Heterogeneity*** and ***Methodological Heterogeneity*** describe the variations in the population, intervention and study factors.[2,3]
  - ***Statistical heterogeneity*** is discussed later
- A ***pooling decision tree*** guides consideration of these factors in the decision to combine trials.

2. Berlin JA, Crowe BJ, Whalen E, et al. Meta-analysis of clinical trial safety data in a drug development program: Answers to frequently asked questions. Clin Trials. 2013;10(1):20-31. http://dx.doi.org/10.1177/174077451246549 5 8.

3. Gagnier JJ, Morgenstern H, Altman DG, et al. Consensus-based recommendations for investigating clinical heterogeneity in systematic reviews. BMC Med Res Methodol. 2013;13(1):106. http://dx.doi.org/10.1186/1471-2288-13-106

Pooling decision tree: Step A



Step A: Explore clinical and methodological heterogeneity

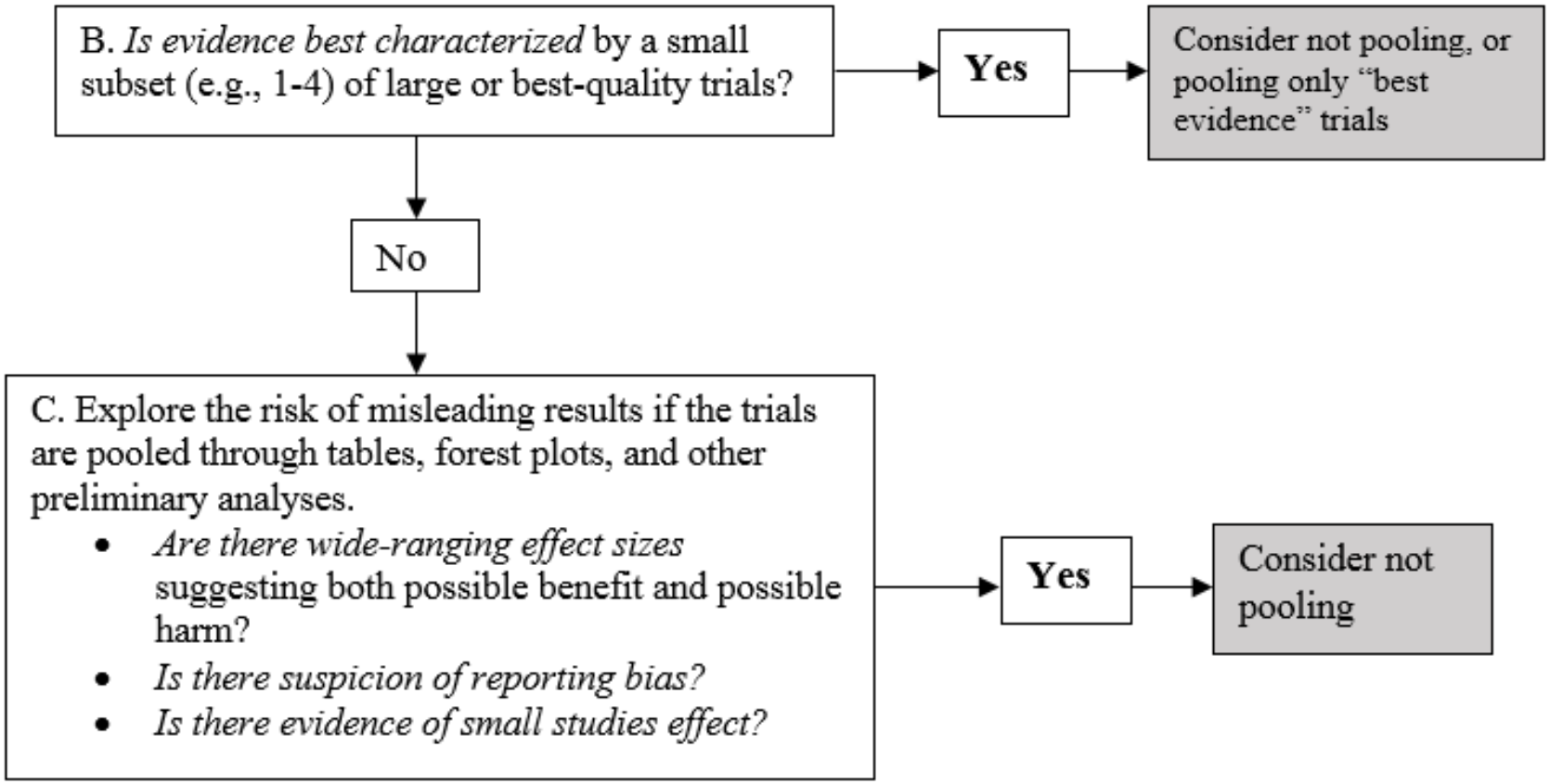
- **Step A: Exploring clinical and methodological heterogeneity of identified studies.**
  - The goal is to identify groups of trials that are similar enough that an average effect is a sensible summary
  - There is no objective measure or consensus standard
- It is recommended to explore variability:
  - Clinical intervention
  - Control condition
  - Participants
  - Study design
  - Outcome
  - Follow-up time

Heterogeneity

- ***Clinical heterogeneity*** relates to participants, interventions, outcomes, study setting.
- ***Methodological heterogeneity*** relates to study methods (e.g., study design, measures, conduct).
  - E.g., can individually-randomized studies be combined with cluster-randomized studies?
  - Often yes, if adjusted for clustering[4]
  - If results systematically differ between the two, then subgroups are more appropriate

4. Thomas J, Askie LM, Berlin JA, Elliott JH, Ghersi D, Simmonds M, Takwoingi Y, Tierney JF, Higgins HPT. Chapter 22: Prospective approaches to accumulating evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Pooling decision tree: Steps B and C



Pooling decision tree: Steps B and C

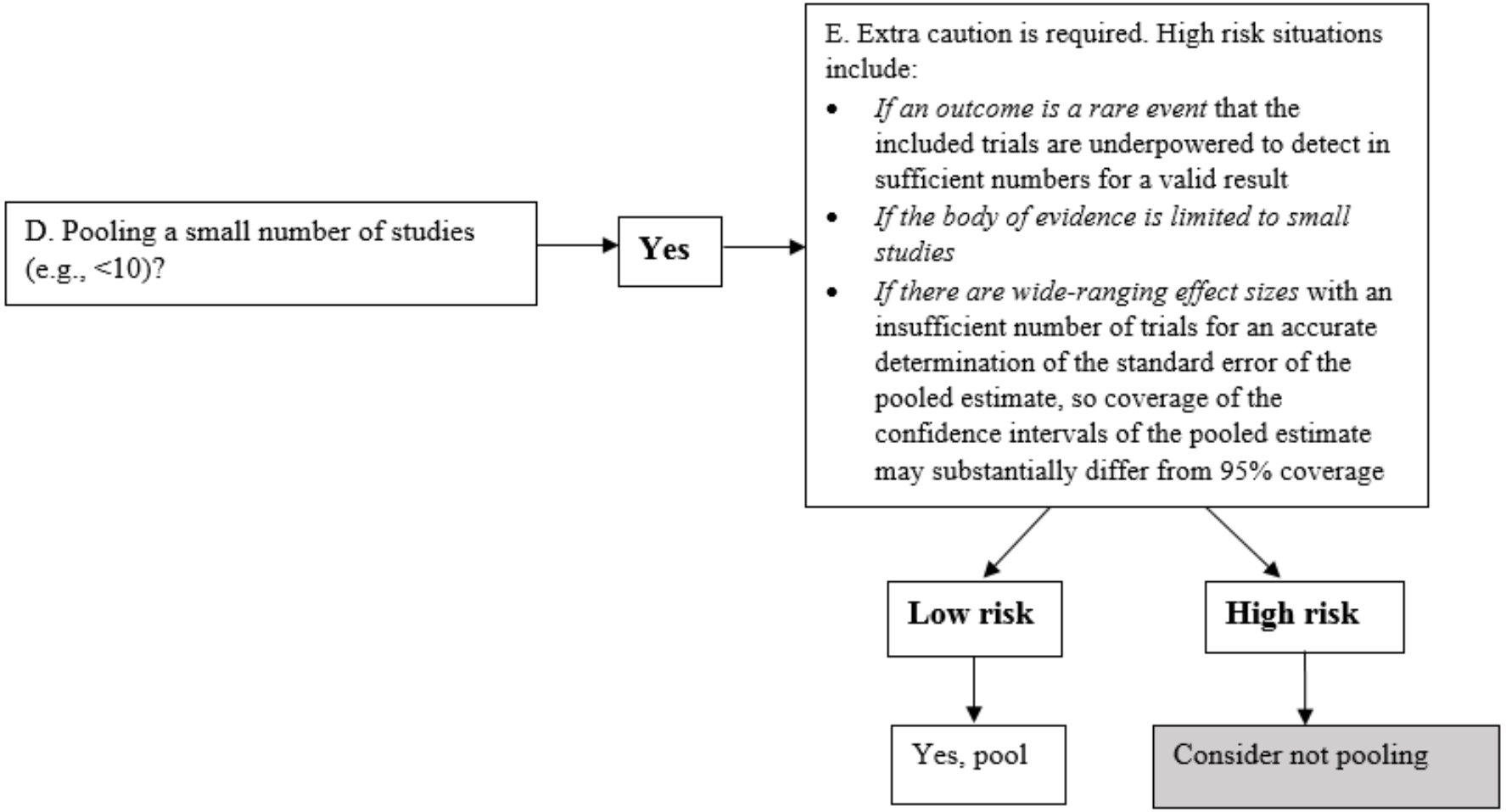
- **Step B: Best evidence or all evidence?**
  - Cherry-picking studies to include in meta-analysis can introduce bias. Decisions to exclude trials because of subjective quality assessments must be justified carefully.
- **Step C: Will combining evidence produce misleading results?**
  - An unmeasured source of heterogeneity may also explain widely varying results.
  - If an intervention truly benefits some patients and harms others, a summary estimate of effect may be meaningless.

Publication bias, reporting bias

- If trials with null results are not published, this results in ***publication bias***.
- If trial results are published only in part, this results in ***reporting bias***.
- These missing results introduce bias into meta-analysis and reduce precision.[5]
  - Use standard tests (e.g., Egger test) to examine small study effects if number of trials permits (i.e., >10)
  - Do not report meta-analysis results that result from small study effects due to bias. (Instead, describe the evidence you are relying on to determine that the results would be biased.)

5. Schmid CH. Outcome reporting bias: a pervasive problem in published meta-analyses. American Journal of Kidney Diseases. 2016 2016;69(2):172-4.

Pooling decision tree: Steps D and E

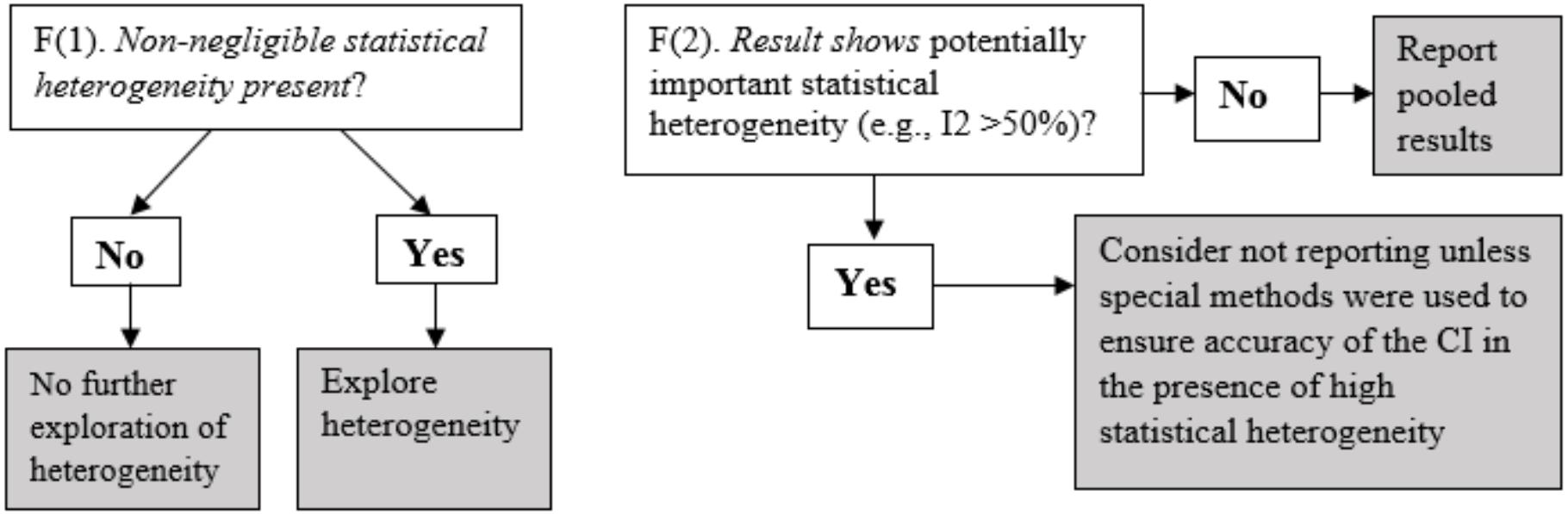


Steps D and E: Small number of studies

- **Steps D & E: Consider these high risk of bias situations when pooling a small number of studies:**
  - ***Small sample sizes:*** Results from small trials are less reliable even when risk of bias is low.[6]
    - If sample sizes are small, pooled effects are less likely to reflect true effects
  - ***Rare outcomes:*** If included trials are underpowered for a valid result, do not pool.[7]
    - Consider calculating the Optimal Information Size to see if combined studies have sufficient power
  - ***Wide-ranging effect sizes:*** Statistical heterogeneity is under-estimated with few studies (especially <7).[8]

6. Bowater RJ, Escarela G. Heterogeneity and study size in random-effects meta-analysis. J Appl Stat 2013;40(1):2-16. https://doi.org/10.1080/02664763.2012.700448
7. Turner RM, Bird SM, Higgins JP. The Impact of Study Size on Meta-analyses: Examination of Underpowered Studies in Cochrane Reviews. PloS One. 2013;8(3):e59202. http://dx.doi.org/10.1371/journal.pone.0059 202
8. Kontopantelis E, Reeves D. Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. Stat Methods Med Res. 2012;21(4):409-26. http://dx.doi.org/10.1177/096228021039200 8

Pooling decision tree: Step F



Step F: Statistical heterogeneity

- **Step F: Consider *statistical heterogeneity* next if clinical and methodological heterogeneity are not concerns.**
  - Chapter 4 covers statistical heterogeneity in detail
- Statistical heterogeneity is assessed by conducting a preliminary meta-analysis.[9]
  - Then decide whether meta-analysis results should be presented, or just forest plots without pooled results
  - Methods for assessing: I^2, Cochrane's Q, and τ^2

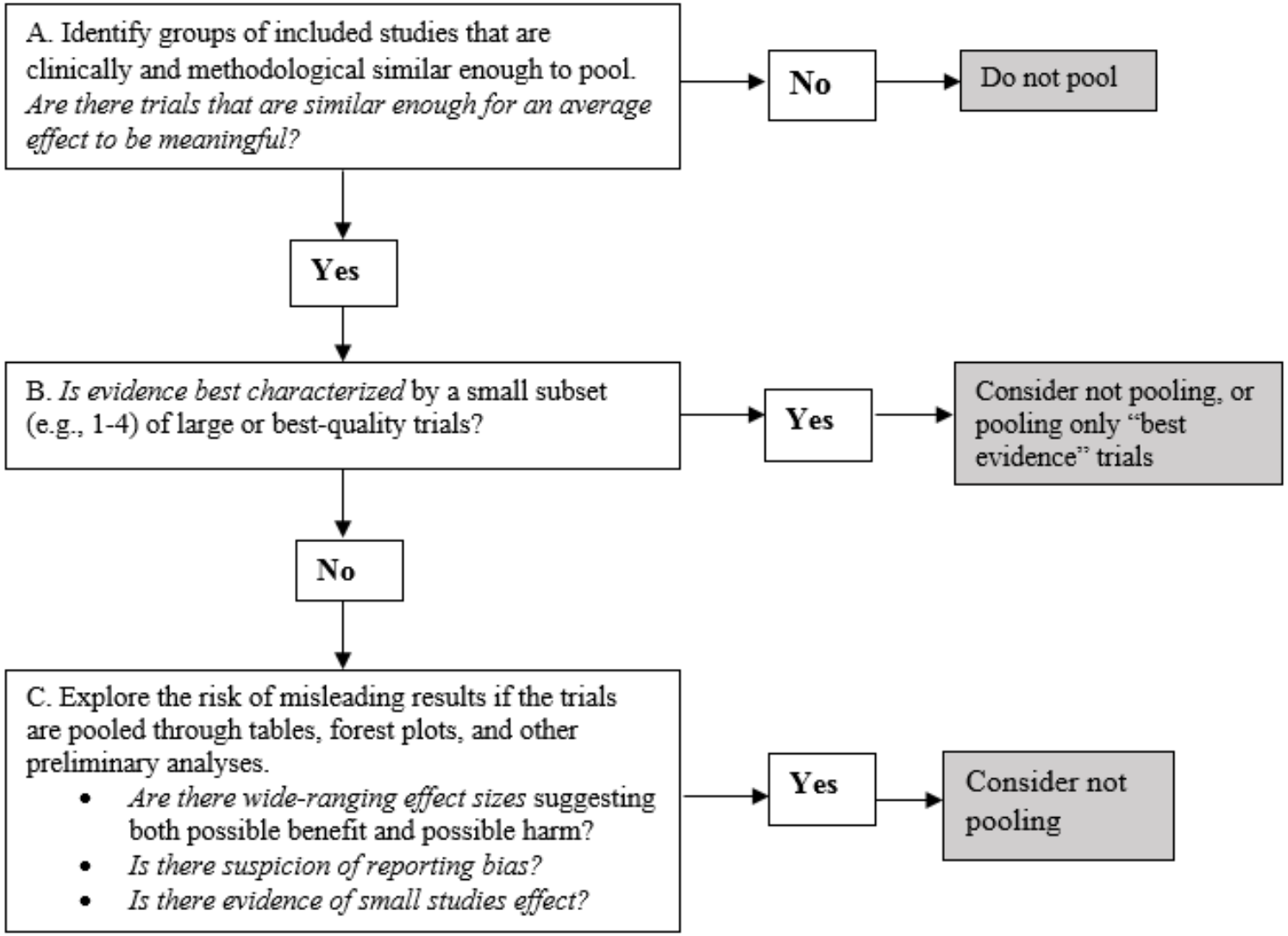
9. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Assessing statistical heterogeneity

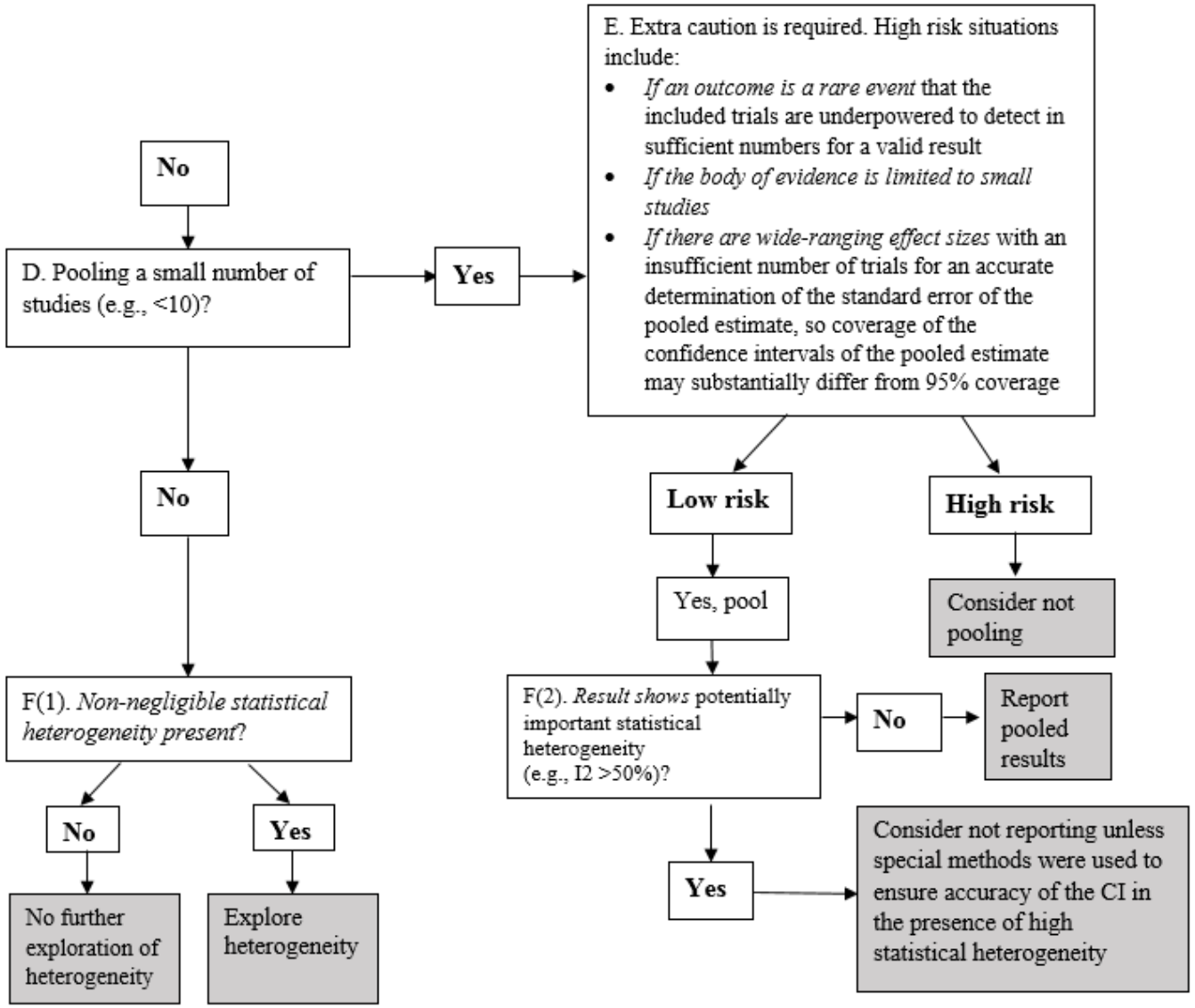
- **I^2:** proportion of total variance in pooled trials due to inter-study variance (i.e., not random).
  - 0-40%: might not be important; 30-60%: may represent moderate heterogeneity; 50-90%: may represent substantial heterogeneity; 75-100%: considerable heterogeneity[9]
  - Critiques of I^2: Underestimates heterogeneity in random effects models; increases as sample size increases; unreliable if too few studies
- **Cochrane's Q and τ^2:** no standardized scale.
- No method is perfect and no method can make the determination of whether to pool alone.

9. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Pooling decision tree (1)



Pooling decision tree (2)



Recommendation for Chapter 1. Decision to combine trials

- Use the pooling decision tree (shown in slides 19 and 20) when deciding whether to combine data.

Author

- This presentation was prepared by Jonathan Snowden, Ph.D.
- The presentation is based on the chapter entitled “Decision to Combine Trials” in the Methods Guide for Comparative Effectiveness Reviews (available at: https://doi.org/10.23970/AHRQEPCMETHGUIDE3

References

1. Verbeek J, Ruotsalainen J, Hoving JL. Synthesizing study results in a systematic review. Scand J Work Environ Health. 2012;38(3):282-90. http://dx.doi.org/10.5271/sjweh.3201

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7. Turner RM, Bird SM, Higgins JP. The Impact of Study Size on Meta-analyses: Examination of Underpowered Studies in Cochrane Reviews. PloS One. 2013;8(3):e59202. http://dx.doi.org/10.1371/journal.pone.0059 202

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