

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

AHRQ

Quantitative Synthesis

Learning Objectives and Recommendations

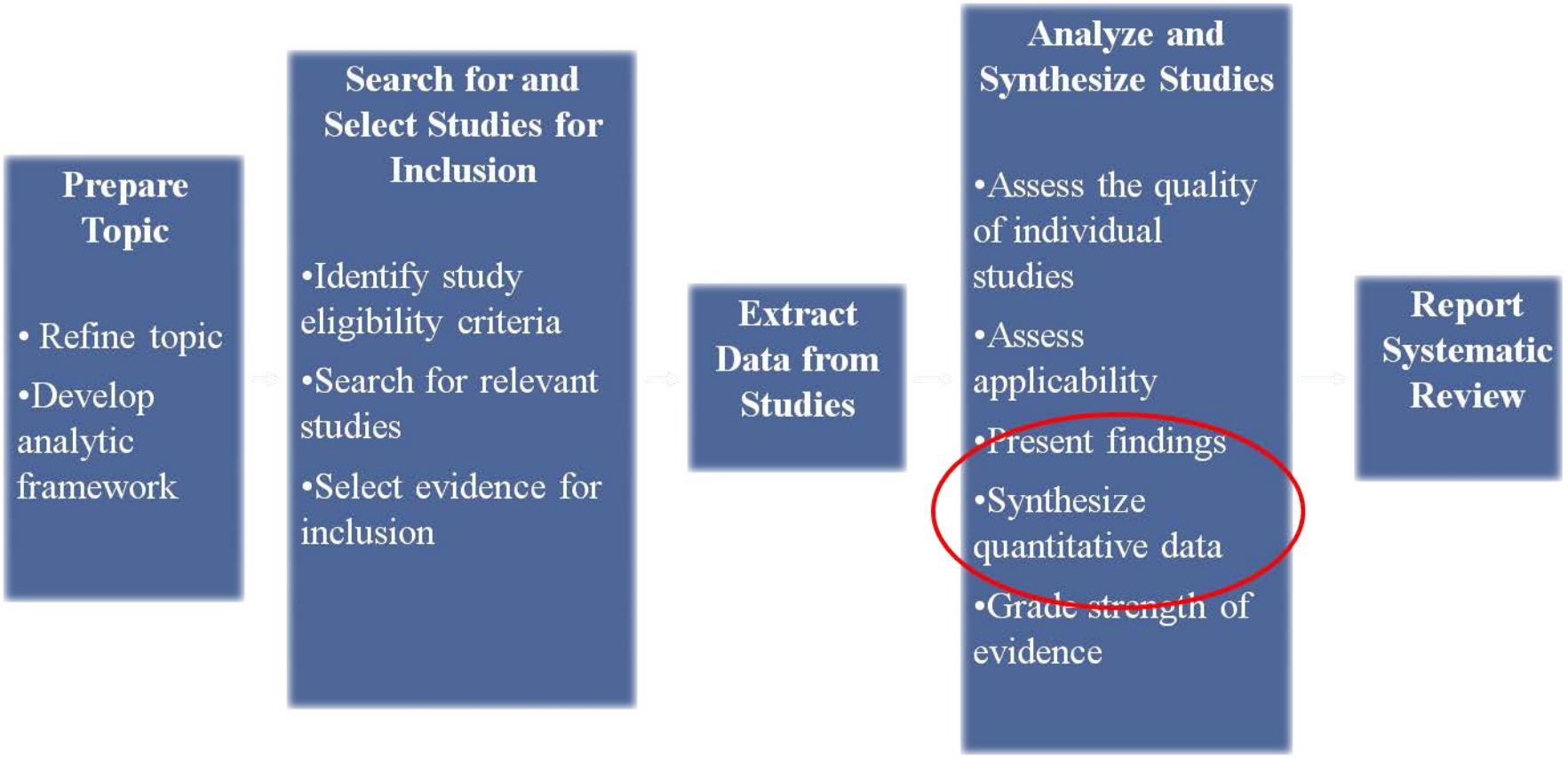
Background

- 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 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.
- More details on individual chapters can be found here: [Link]

Systematic review process overview



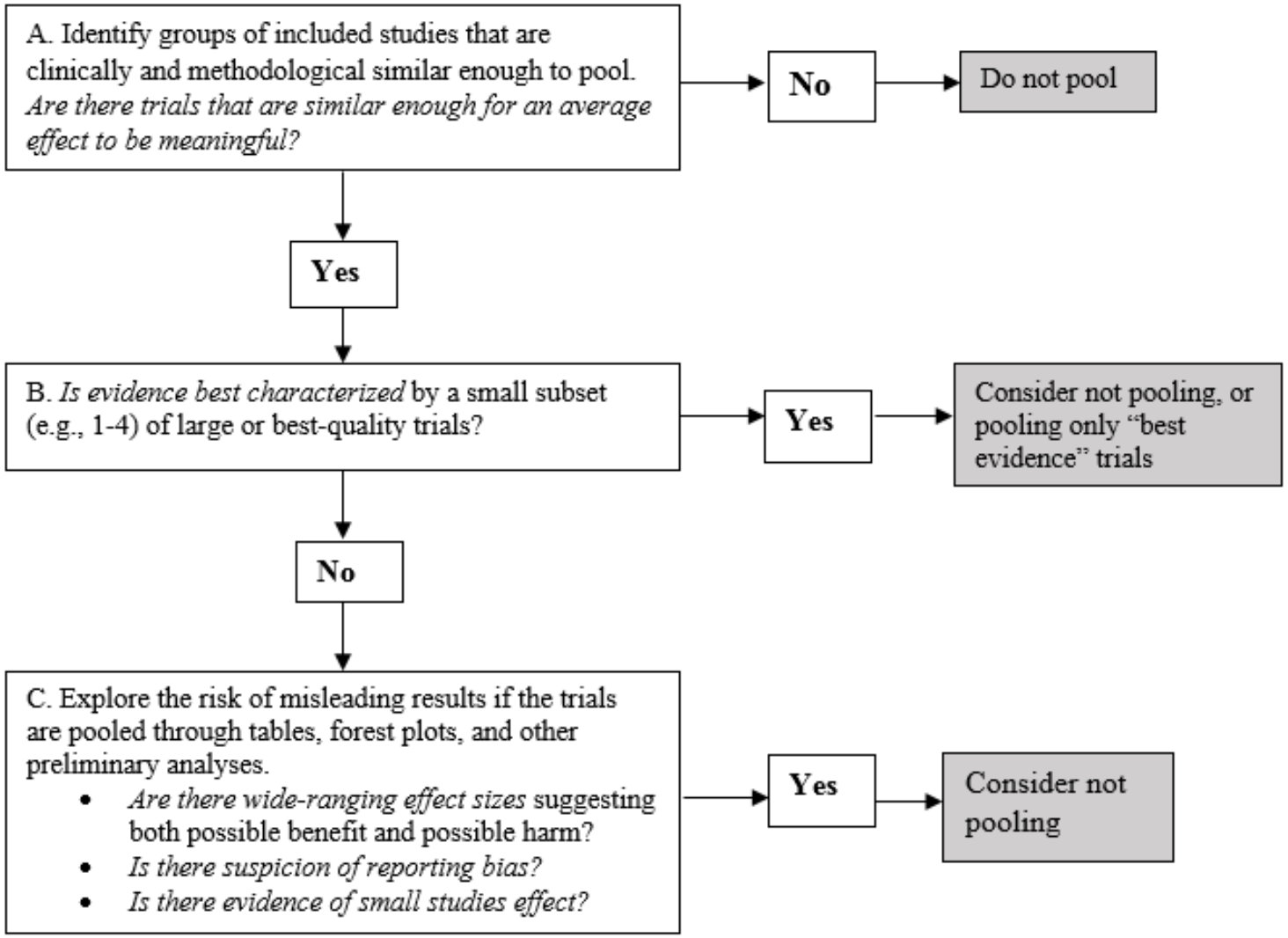
Learning objectives

- **Chapter 1:** Be able to describe the basic principles of combining data and when this is appropriate.
- **Chapter 2:** Be able to recognize common measures of association for meta-analysis (e.g., risk difference, odds ratio).
- **Chapter 3:**
  - 1. Be able to describe a scenario for which a fixed effects versus random effects model may be appropriate.
  - 2. Be able to list different types of estimators for random effects models.
  - 3. Be able to describe the strengths and weaknesses for each of the estimators for different types of data.
- **Chapter 4:** Be able to distinguish between (1) clinical and methodological heterogeneity, and (2) statistical heterogeneity.
- **Chapter 5:** Be able to understand the network meta-analysis approach and when it can be implemented

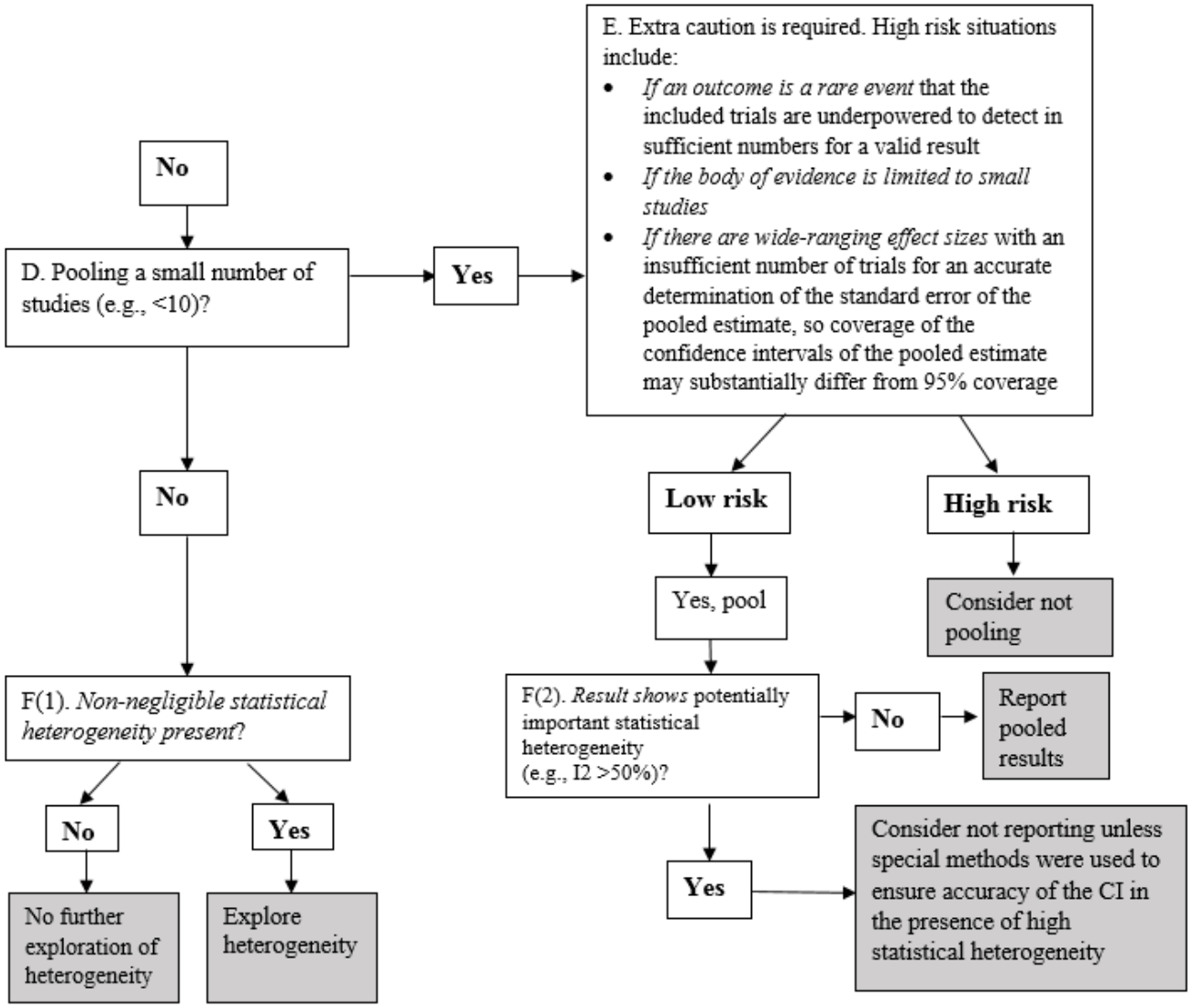
Recommendation for Chapter 1: Decision to combine trials

- Use the pooling decision tree on subsequent slides when deciding whether to combine data.

Pooling Decision Tree (1)



Pooling Decision Tree (2)



Recommendations for Chapter 2. Different effects for different data types

- **For binary outcomes:**
  - Consider carefully which binary measure to analyze.
  - Risk difference is the preferred measure if conversion to NNT or NNH is sought.
  - Risk ratio and odds ratio are likely to be more consistent than the risk difference when studies differ in baseline risk.
  - Risk difference is not the preferred measure when the event is rare.
  - Risk ratio is not the preferred measure if switching between occurrence and non-occurrence of the event is important to the meta-analysis.
  - The odds ratio can be misleading.
- **For continuous outcomes:**
  - When studies use the same metric, mean difference is preferred measure.
  - When calculating standardized mean difference, Hedges' *g* is preferred over Cohen's *d* due to the reduction in bias.
- **General:**
  - If baseline values are unbalanced, perform an ANCOVA analysis. If ANCOVA cannot be performed and the correlation is greater than 0.5, change from baseline values should be used to compute the mean difference.
    - If the correlation is less than or equal to 0.5, follow-up values should be used.
  - Data from clustered randomized trials should be adjusted for the design effect.

Recommendations for Chapter 3. Statistical models for meta-analysis

- PL method appears to generally perform best. The DL method is also appropriate when between-study heterogeneity is low.
- **For study-level aggregated binary data and count data**, use of a generalized linear mixed effects model assuming random treatment effects is also recommended.
- **For rare binary events:**
  - Avoid methods that use continuity corrections.
  - For studies with zero events in one arm, or studies with sparse binary data but no zero events, obtain an estimate using the Peto method, the Mantel-Haenszel method, or a logistic regression approach, without adding a correction factor, when the between-study heterogeneity is low.
  - When the between-study heterogeneity is high, and/or there are studies with zero events in both arms, more recently developed methods such as a beta-binomial model could be explored and used.
  - Conduct sensitivity analyses with acknowledgement of the inadequacy of data.
- If choosing Bayesian methods, use of vague priors is supported.

Recommendations for Chapter 4. Statistical heterogeneity

- Expect, visually inspect, quantify, and sufficiently address statistical heterogeneity in all meta-analyses.
- Include prediction intervals in all forest plots.
- Consider evaluating multiple metrics of heterogeneity, between-study variance, and inconsistency (i.e., Q, τ^2 and I^2 along with their respective confidence intervals when possible).
- A non-significant Q should not be interpreted as the absence of heterogeneity, and there are nuances to the interpretation of Q that carry over to the interpretation of τ^2 and I^2.
- Random effects is the preferred method for meta-regression that should be used under consideration of low power associated with limited studies (i.e., <10 studies per study-level factor) and the potential for ecological bias.
- A simplified two-step approach to control-rate meta-regression that involves scatter plotting and then hierarchical or Bayesian meta-regression is recommend.
- Routine use of multivariate meta-analysis not recommended.

Recommendations for Chapter 5. Network meta-analysis

- Always base a network meta-analysis on a rigorous systematic review.
- **For a network meta-analysis, three assumptions must be met :**
  - Homogeneity of direct evidence
  - Transitivity, similarity, or exchangeability
  - Consistency (between direct and indirect evidence)
- Investigators may choose a frequentist or Bayesian mode of inference based on the research team's expertise, complexity of evidence network, and the research question.
- **Evaluating inconsistency** is a major and mandatory component of network meta-analysis.
  - Conducting a global test should not be the only method used to evaluate inconsistency. A loop-based approach can identify the comparisons that cause inconsistency.
- **Cautiously use inference based on the rankings and probabilities of treatments being most effective.**
  - Rankings and probabilities can be misleading and should be interpreted based on the magnitude of pairwise effect sizes. Despite such rankings, differences across interventions may not be clinically important.

Resources for Chapter 1

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