



AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

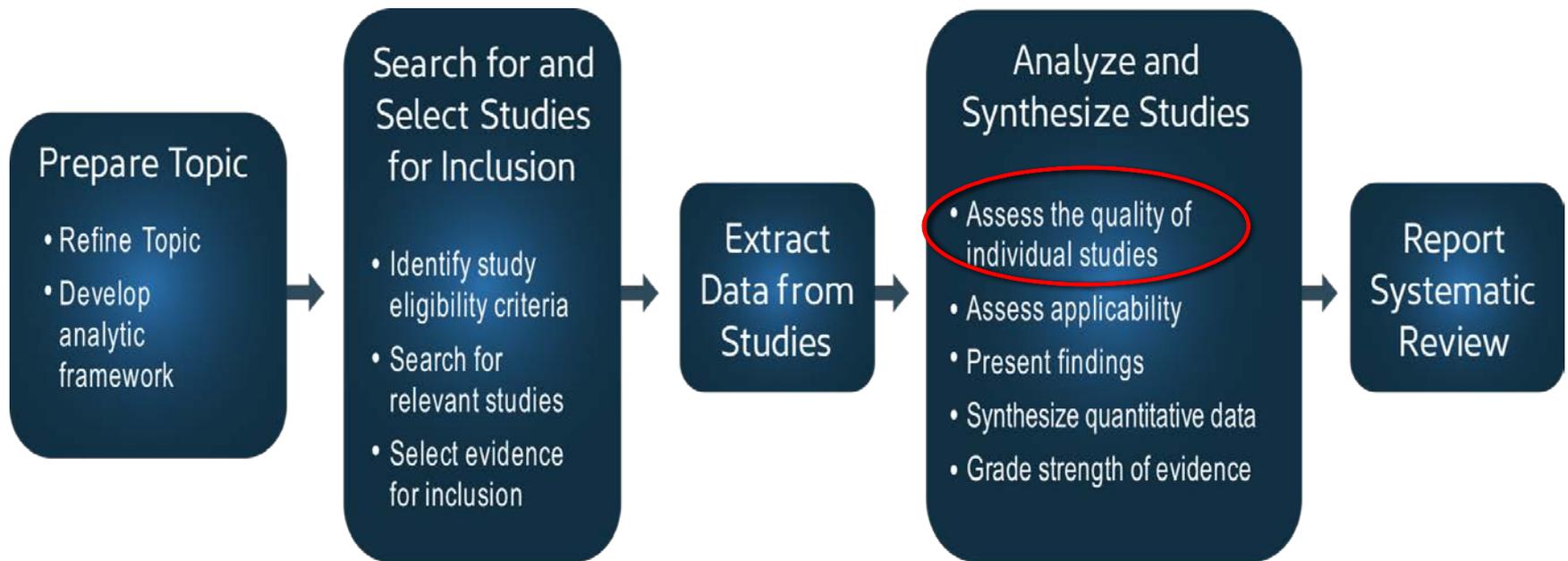


Assessing the Risk of Bias in Systematic Reviews of Health Care Interventions

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The Agency for Healthcare Research and Quality (AHRQ)
Training Modules for Systematic Reviews Methods Guide
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Systematic Review Process Overview



Learning Objectives

At the conclusion of this lecture the successful learner will be able to:

- Describe the importance of determining the risk of bias
- Identify the stages an EPC should use in assessing risk of bias and what needs to be done at each stage
- Describe factors that create risk of bias and what category of bias the study can be assigned

Introduction

- Not all studies are created equal
 - ▶ Limitations based on methodological features
 - ▶ Studies with weaknesses are less persuasive
- Assessing risk of bias helps interpret findings and explain heterogeneity
- Some EPC reviews exclude high risk of bias studies while others include them

Defining Risk of Bias

- Risk of bias is:
 - ▶ An assessment of the internal validity of the individual studies that inform systematic review key questions
 - ▶ Assessing the risk that the results are skewed by bias in study design or execution
- Risk of bias is not:
 - ▶ Assessing the degree of congruence between research questions and designs of included studies
 - ▶ The precision of an effect estimate
 - ▶ Applicability of the evidence

Using Risk of Bias Assessment Conducted in Previous Reviews

- When using an existing systematic review in a new systematic review or subgroup analyses:
 - ▶ The risk of bias assessment from the existing systematic review may be used if deemed acceptable
 - ▶ If not, a risk of bias assessment still needs to be done at the individual study level

Stages in Assessing Risk of Bias

1. Develop Protocol
2. Pilot test and train
3. Perform Assessment of Risk of Bias of Individual Studies
4. Use Risk of Bias Assessments in Synthesizing Evidence
5. Report Risk of Bias Findings, Process and Limitations

Stage 1. Develop Protocol

- Specify risk-of-bias categories and criteria and explain their inclusion
- Select and justify choice of specific risk-of-bias rating tools, including validity of selected tools
- Explain how individual risk-of-bias categories (or items from a tool) will be presented or summarized
- Explain how inconsistencies between pairs of risk-of-bias reviewers will be resolved
- Explain how the synthesis of the evidence will incorporate assessment of risk of bias



STAGE 1 SPECIAL CONSIDERATIONS

Develop Transparent and Reproducible Methodology

- The protocol should include clear definitions of the types of biases that will be assessed and a priori decision rules for assigning the risk of bias for each individual study
- New or changed processes developed over the course of the review should be documented clearly

Move Beyond Study Design Label

- Do not rely solely on study design label (e.g., randomized controlled trial [RCT]) as a proxy for assessment of risk of bias
 - ▶ Not all trials designated as randomized truly meet the definition (e.g. every other person allocated to intervention)
 - ▶ Not all trials designated as double-blind truly meet the definition (e.g. the drug is a gelatin capsule but the placebo is a tablet)
 - ▶ A randomized controlled trial can have other features that introduce risk of bias (e.g. substandard methods to measure outcome)

Determine Whether a Single Risk of Bias Rating for a Study Suffices



- You must make sure that your criteria and forms are set up to allow for different ratings by outcomes
- Risk-of-bias ratings for a study may vary according to outcome
 - ▶ Some outcomes may be well defined and properly measured, others may not

Consider Many Sources of Bias

- When selecting risk of bias categories, consider:
 - ▶ Bias arising in the randomization process or due to confounding
 - ▶ Departures from intended interventions
 - ▶ Missing data
 - ▶ Low quality measurement of outcomes
 - ▶ Selective outcome reporting in all studies
 - ▶ Biased participant selection and misclassification of interventions

Choose Instrument for Assessing Risk of Bias

- Choose instruments based on epidemiological study design principles and established measurement properties (e.g., reliability, internal consistency) or empirical evidence
- Choose instruments that assess specific concerns related to each of the risk of bias categories that pose threats to the accuracy of the effect estimate

What should be done when elements of RoB are not explicitly reported?

- Studies should be assessed on their design-specific criteria and conduct rather than quality of reporting of methods and results
 - ▶ EPCs may explore grey literature sources like the FDA website or ClinicalTrials.gov to find protocol details needed for risk of bias assessment but not available in articles
 - ▶ EPCs may contact authors to identify missing details needed for risk of bias assessment but not available in articles
- Poorly reported studies may be judged as unclear risk of bias

Stage 2. Pilot Test and Train

- Determine composition of the review team
 - ▶ Dual independent assessment of risk of bias with an unbiased reconciliation method
- Reviewers must be trained
- Pilot test assessment of risk-of-bias tools using a small subset of studies
- Identify issues and revise tools or training as needed

Stage 3. Perform Assessment of Risk of Bias of Individual Studies (I)



- Specify a “target” trial to assist in considering bias sources
- Categorize study design of each individual study
 - ▶ Example: randomized, cohort, prospective step-wedge
- For randomized studies, clarify if effect of interest is intention-to-treat or per-protocol
- For nonrandomized studies, specify likely sources of potential confounding
 - ▶ Consider making judgments about each risk-of-bias category, using the preselected appropriate criteria

Stage 3. Perform Assessment of Risk of Bias of Individual Studies (II)



- Present judgment criteria on individual categories or items or as a summary for each outcome
- If presenting a summary, make judgments about overall risk of bias for each included outcome of the individual study, considering study conduct
 - ▶ Rate as low, moderate, high, or unclear risk of bias within study design; document the reasons for judgment and process for finalizing judgment
- If separately presenting risk-of-bias for individual items, assess implications for direction and magnitude of bias
 - ▶ Resolve differences in judgment and record final rating for each outcome
- When determining an overall rating for an individual study, determine a method *a priori* and clearly report how overall scores were calculated

Stage 4. Use Risk of Bias Assessments in Synthesizing Evidence (I)

- If you use *a priori* criteria for including or excluding studies based on risk-of-bias assessments, conduct sensitivity analysis
- Synthesize individual study risk of bias into overall strength of evidence study limitations domain
- Consider the impact of the major study limitations identified and how they may interact
- Consider conducting additional analyses to assess impact of risk of bias on findings

Stage 4. Use Risk of Bias Assessments in Synthesizing Evidence (II)

- Consider direction and magnitude of possible bias on effect estimate (when possible)
- When summarizing evidence, consider conducting sensitivity analyses to evaluate whether including studies with high or unclear risk of bias influences estimates of effect or heterogeneity
- Use risk of bias assessments to explore heterogeneity and grade strength of evidence

Stage 5. Report Risk of Bias Findings, Process and Limitations

- Describe the risk-of-bias process, post-protocol deviations, and limitations to the process
- Balance competing considerations of simplicity of presentation and burden on the reader when presenting results of risk of bias assessments
 - ▶ Categorization without details is simple but not transparent
- Systematic reviewers excluding high risk-of-bias studies from analyses should base their decision to do so on sensitivity analyses
- Avoid presentation of risk of bias assessment solely as a number

Key Messages

- Risk of bias is an important consideration in whether to use a study or how the study should be analyzed, used, or interpreted
- There are several distinct steps in the risk of bias assessment process that need to be conducted in sequence
- Developing a protocol *a priori* that delineates how studies will be assessed for risk of bias and how the risk of bias determinations will influence the analysis and interpretation of the results
- A dual determination process is recommended to minimize uncertainty
- Transparent reporting of risk of bias is critical but must balance completeness and burden to the reader

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