



AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

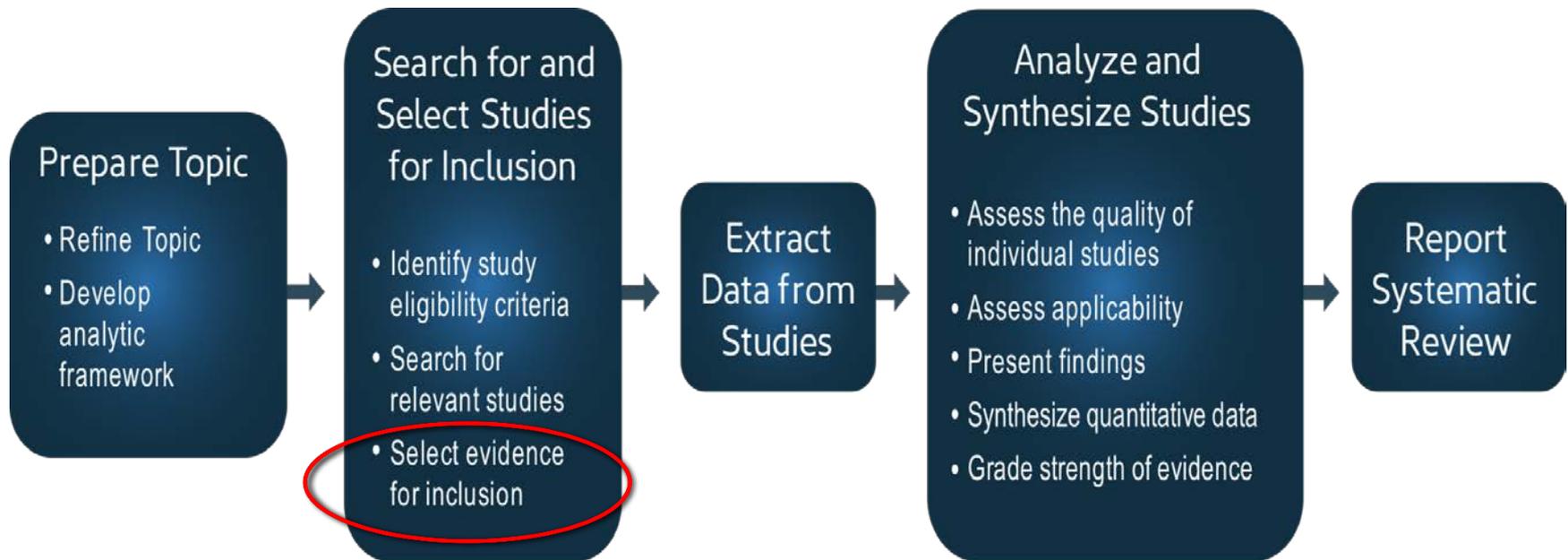


Prioritization and Selection of Harms for Inclusion in Systematic Reviews

Prepared for:

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

Systematic Review Process Overview



Learning Objectives

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

- Describe a process to identify and prioritize potential harms
- Identify the types and number of harms to include for treatments and diagnostic tests
- Describe when it is acceptable to add harms not selected *a priori*
- Describe how to transparently report methods used to select harms

Harms are Adverse Events or Complications



- Definition of harms:
 - ▶ Adverse events or complications of drugs, dietary supplements, surgery, devices, or other procedures

Chou R. *Ann Intern Med.* 2005;142(12 Pt 2):1090-9

Selecting Harms Outcomes Poses Challenges



- EPC reviews frequently address many interventions, which could result in many potential harms to review
- Different interventions for the same condition are frequently associated with a large number of diverse harms
- Studies may report composite harms
- Harms not specified in the original protocol may be encountered during the review process
- Reviewing all potential harms is not feasible and could make it difficult for users of EPC reviews to reach conclusions

Recommendations Based on Rigorous Methods



- Working group of 12 methodologists from AHRQ and AHRQ EPCs created recommendations based on:
 - ▶ Results of literature search
 - ▶ Review of EPC reports
 - ▶ Key informant panel feedback

Recommendations Overview (I)

1. Identify harms of greatest importance
2. Use prioritization process to narrow number of harms
3. Select the most appropriate process
4. Methods used to prioritize harms should be concordant with benefits
5. Routinely include serious or common and bothersome individual harms

Recommendations Overview (II)

6. Consider composite harms endpoints
7. Check diagnostic tests for imprecision or insensitivity
8. Aim for 5-10 individual or composite harms
9. Have good rationale for assessing harms post-hoc
10. Report on important included and excluded harms



Prioritization of Harms

1. Identify Harms that are of Greatest Importance (I)

- EPC reviews should assess harms most important to decision-makers including clinicians, patients, and stakeholders
- Create comprehensive list of potential harms
- Categorize/assess the importance of harms outcomes
 - ▶ Important = serious or common and bothersome

1. Identify Harms that are of Greatest Importance (II)

- Serious denotes death, life threatening, hospitalization, prolonging hospitalization, persistent or incapacitating symptoms, or result in congenital anomalies or birth defects
- Common and bothersome denotes the most common harms that inconvenience the patient
- An exception to this rule is if a review is designed to focus on less important but specific pre-defined potential harm or harms

2. Use Prioritization Process to Narrow Number of Harms

- Prioritize the important harms with those of greatest importance at the top of the list
 - ▶ Unless the harms are serious or common and bothersome, they can usually be disregarded
 - ▶ May not be feasible to include all important harms

3. Select an Appropriate Prioritization Process (I)



- The specific prioritization process used can vary
- Patient and stakeholder feedback should be obtained to help prioritize harms
- The prioritization may be formal or informal
- Formal process:
 - ▶ GRADE has a formal process for prioritizing outcomes, including benefits and harms
 - ▶ Delphi panels can be constructed with a formal process
 - ▶ Unclear benefits over less formal process

Garces JPD. *Mayo Clinic* 2012.

Montgomery A. *Qual Health Care* 2001;10.

3. Select an Appropriate Prioritization Process (II)



- Informal process
 - ▶ Literature or regulatory agency review for incidence or severity data
 - ▶ Input or informal interviews with experts in the field, patients, and other stakeholders

Garces JPD. *Mayo Clinic* 2012.

Montgomery A. *Qual Health Care* 2001;10.

One Possible Approach: GRADE Outcome Selection



- Grading of Recommendations Assessment, Development and Evaluation (GRADE) Group recommends beneficial and harmful outcomes get prioritized through solicitation of panel member and stakeholder input
 - ▶ Outcomes rated for importance via 1-9 numerical rating system
 - ▶ Outcomes rated highest priority are included
- GRADE recommends that summary of findings tables should focus on no more than 7 outcomes
- EPC authors consider this one of many acceptable processes but may be necessary to consider more than 7 outcomes

4. Methods Used to Prioritize Harms Should be Concordant with Benefits

- The principles underlying the prioritization of outcomes, either beneficial or harmful, should be similar
- It may be difficult to discern a harm from a failed treatment
- If intervention was intended to reduce a final health outcome, the occurrence of the outcome is a failed event, not an adverse event.



Types of Harms to Include



5. Serious or Common and Bothersome Individual Harms (I)

- Individual harms (e.g. heart attacks, diarrhea, seizure)
- Not all important individual harms need to be included
 - ▶ Some harms are so well established that including them in a systematic review is not needed
- Some EPC reviews are designed to focus on one particular harm

5. Routinely Include Serious or Common and Bothersome Harms (II)

- Reviews should give priority to final (mortality, morbidity, quality of life, or function) over intermediate (laboratory values of physiological parameters) health outcomes
- Reviewers should consider intermediate harms outcomes when data on associated final health outcomes are sparse and the association between the two are well established

6. Consider Composite Adverse Events (I)

- Composite harms define the incidence of people experiencing one of several possible harms such as Major Adverse Cardiovascular Events (MACE), comprising myocardial infarction, stroke, cardiovascular death, or target vessel revascularization
- Composite adverse events can help facilitate comparisons across interventions

6. Consider Composite Adverse Events (II)

- “Serious adverse events” or “withdrawal due to adverse events” may be particularly useful
 - ▶ It is harder to interpret clinical meaningfulness of less severe composite harms
- Interpret composite endpoints by assessing the individual harms that constitute them
- Record definitions of composite harms

7. Check diagnostic tests for Imprecision or insensitivity

- Diagnostic tests (e.g. genetic or hematologic testing, scanning, functional tests) can cause harms
- Can a diagnostic test cause a harm?
 - ▶ Nonspecific diagnostic tests can lead to false positives that may precipitate further unneeded testing, over-diagnosis, or over treatment
 - ▶ Insensitive diagnostic tests can lead to false negative that may prevent timely treatment for diseases best handled at earlier stages

Number of Harms to Include, Adding Harms, and Reporting Harms

8. Aim for 5 to 10 Individual or Composite Harms

- How many harms should you include?
 - ▶ GRADE working group suggests limiting to 7 total outcomes for benefit and harms, although some may feel this is overly restrictive
 - ▶ 5-10 individual or composite harms should be sufficient for most EPC reviews comparing two interventions (e.g. drug A vs. drug B)

9. Have good rationale for assessing harms post-hoc

- Harms not selected a priori might come to be seen as having great importance during the review (e.g. new published data or new regulatory action)
 - ▶ Add harm as a protocol modification with rationale
 - ▶ Interpret newly included harms with same due diligence as those selected *a priori*
 - Plausibility of biological effect, pharmacokinetic and dynamic data, magnitude of effect, precision of estimate, statistical significance of findings

10. Reporting on Important Included and Excluded Harms

- Reporting transparently is important
- The prioritized list of harms should be included in the summary of evidence tables
- Using a prioritization process strengthens the rationale for the harms included and for those excluded
 - ▶ Specify the prioritization process (formal or informal)
 - ▶ Differentiate serious from common/bothersome harms
 - ▶ Provide reason why a serious harm was excluded
 - Possible reasons: causality is weak, review is scoped to focus on another specific harm or harms

Key Messages

Key Messages (I): Harms are Important But Not All Can be Included



- Harms are vitally important to determine the net benefit or balance of benefit and harms of an intervention
- Not every harm can be assessed, but as a general guideline, 5-10 harms may be appropriate for a comparison between 2 interventions
 - ▶ Multiple comparisons within a review may evaluate overlapping harms

Key Messages (II): Harms Should Be Classified, Prioritized, and Properly Reported



- Create a list of all harms and categorize/assess their importance
 - ▶ Important harms are severe or common and bothersome
 - ▶ Prioritize important ones using a formal or informal process
 - ▶ Have key stakeholders, including patients, provide key input into priority rankings
- Transparently report on the important harms included or not with a rationale for selection and differentiate serious from common or bothersome harms

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