PCORI Methodology Standards: Academic Curriculum
Module 8: Step 6—Summarize and Synthesize Evidence

Category 11: Systematic Reviews

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Step 6: Summarize and Synthesize Evidence

- Assemble evidence tables
  - Reassess priorities
  - Exclude duplicative data

- Prepare qualitative and/or quantitative summary of evidence
  - Select key effect measures
    - Binary (relative risk, odds ratio, risk difference)
    - Continuous (mean difference, standardized effect size)
  - Assess heterogeneity (clinical or methodological or statistical)

- Consider meta-analysis, meta-regression, and network meta-analysis
  - Direct versus indirect comparisons

- Assess strength of evidence for each important outcome
Two-stage process:
1. For each study, calculate a summary statistic for the observed effect
2. Then, calculate a pooled effect estimate as a weighted average of study-level effects

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

Analysis may assume effects follow a distribution across studies (random effects) or that each study estimates the same effect (fixed effect)
- Special methods may be needed for rare outcomes

Use standard error of pooled effect estimate to calculate a 95% confidence interval for degree of certainty about the estimate

Use variation in results between studies to assess consistency of effects across studies
- Include sensitivity analysis
Forest Plots

Estimates with 95% Confidence Intervals

- Kennedy 1997
- Locke 1952A
- Lopes 1997
- Reynolds 1998
- Seiberth 1994

- Line of no effect
- Estimate and confidence interval for each study
- Estimate and confidence for the meta-analysis
- Scale (effect measure)
- Favors light reduction
- Favors control
- Direction of effect
Odds of congestive heart failure with thiazolidinediones and sulfonylureas. Error bars represent 95% CIs. SU = sulfonylurea; TZD = thiazolidinedione.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>TZD</th>
<th>SU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, n</td>
<td>Patients, n</td>
</tr>
<tr>
<td>Agarwal et al, 2005 (58)</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Tolman et al, 2009 (59)</td>
<td>12</td>
<td>1051</td>
</tr>
<tr>
<td>Kahn et al, 2006 (23)</td>
<td>22</td>
<td>1456</td>
</tr>
<tr>
<td>St John Sution et al, 2002 (60)</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Odds Ratio (95% CI)

- Agarwal et al, 2005 (58): 1.00 (0.14 to 7.24)
- Tolman et al, 2009 (59): 1.09 (0.48 to 2.47)
- Kahn et al, 2006 (23): 2.44 (1.12 to 5.32)
- St John Sution et al, 2002 (60): 67.06 (0.00 to 4 × 10^6)
- Overall: 1.68 (0.99 to 2.85)

For systematic reviews, strength (or quality) of evidence is defined as the extent of confidence that an estimate of effect is correct.

Evidence summaries should be used to make judgments transparently about the overall strength of a body of evidence for each important outcome.

Explicit consideration should be given to each of the GRADE domains for evaluating strength of evidence.

Judgments should be expressed using three or four categories based on definitions developed by the GRADE Working Group:
- High, moderate, low (or very low)

## Domains of GRADE Approach to Assessing Strength of Evidence

1. Study limitations or risk of bias
2. Directness
3. Consistency
4. Precision
5. Publication bias

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1. Magnitude of effect
2. Dose-response relationship
3. Residual plausible confounding

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Potential Causes of Bias and Error in Summarizing and Synthesizing Evidence

- **Bias**
  - Improper selection of outcome measures
  - Improper choice of pooling technique
    - Random versus fixed effect
    - Correction factor for zero events
  - Strength of evidence influenced by conflict of interest

- **Error**
  - Mistakes in transferring or pooling data
  - Poor understanding of GRADE approach

- **Bias or error in preceding steps**
Replication of Meta-Analyses for Which Calculated SMD Differed From Authors for at Least One of Two Trials (Seven Meta-Analyses Differed by ≥0.1 for Point Estimate or 95% CI)

Forest Plots of Standardized Mean Difference and 95% CI by 10 Observers for 10 Meta-Analyses

What Can Be Done to Minimize Bias and Error in Summarizing and Synthesizing Evidence?

- Follow established guidance for creating evidence summaries, conducting meta-analysis, and grading strength of evidence
  - Cochrane Collaboration
  - Evidence-Based Practice Center Program
  - GRADE Working Group

- Pay attention to potential causes of bias and error in all steps of the systematic review process
What Can Be Done to Make Systematic Reviews Trustworthy?

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
  - Checklist of 27 items
  - Diagram of flow of information through four review phases
    - Identification, screening, eligibility, included
  - Guiding principles
    - Iterative process
    - Conduct versus reporting of research
    - Importance of reporting biases
    - Study versus outcome level

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Standard 2.1: Establish a team with appropriate expertise and experience to conduct review
- Include expertise in systematic review methods
- Include expertise in quantitative methods
- Include other expertise as appropriate

Standard 2.3: Ensure user and stakeholder input as review is designed and conducted
- Protect independence of team to make final decisions about design, analysis, and reporting

Standard 2.4: Manage bias and conflict of interest for individuals providing input
- Require individuals to disclose conflict of interest and professional or intellectual bias
- Exclude input from individuals whose conflict of interest or bias would diminish credibility in eyes of intended users
Standard 2.6: Develop a systematic review protocol

- Describe context and rationale for review from decision-making and research perspective
- Describe study screening and selection criteria (inclusion and exclusion)
- Describe which outcomes, time points, interventions, and comparisons will be addressed
- Describe search strategy for identifying relevant evidence
- Describe procedures for study selection and data extraction, and how to identify and resolve disagreement between researchers in study selection and data extraction
- Describe approach to critically appraising studies
- Describe method for evaluating body of evidence, including quantitative and qualitative synthesis
- Describe and justify planned analyses of differential treatment effects according to subgroups, how intervention is delivered, or how outcome measured
- Describe proposed timetable
Standard 4.1: Use a prespecified method to evaluate the body of evidence

- For each outcome, systematically assess the following characteristics:
  - Risk of bias
  - Consistency
  - Precision
  - Directness
  - Reporting bias

- For evidence that includes observational research, assess the following characteristics:
  - Dose-response association
  - Plausible confounding that would change the observed effect
  - Strength of association

- For each outcome specified in the protocol, use consistent language to characterize the level of confidence in the estimates of the effect
Standard 4.2: Conduct a qualitative synthesis

- Describe clinical and methodological characteristics of included studies, including size, inclusion of important subgroups, timeliness, and other relevant factors
- Describe strengths and limitations of individual studies and patterns across studies
- Describe in plain terms how flaws in design or execution of the study (or groups of studies) could bias the results, explaining the reasoning
- Describe the relationships between characteristics of studies and their reported findings and patterns across studies
- Discuss the relevance of studies to the populations, comparisons, interventions, settings, and outcomes of interest
Relevant IOM Standards for Summarizing and Synthesizing Evidence

- **Standard 4.3: Decide if, in addition to qualitative synthesis, the review will include quantitative analysis**
  - Explain why a pooled estimate might be useful to decision makers

- **Standard 4.4: If conducting a meta-analysis, do the following:**
  - Use expert methodologists to develop, execute, and peer review the analysis
  - Address heterogeneity among study effects
  - Accompany all estimates with measures of statistical uncertainty
  - Assess sensitivity of conclusions to changes in the protocol, assumptions, and study selection
**Standard 5.1: Prepare final report using a structured format**
- Title, abstract, executive summary, and summary for lay public
- Introduction: rationale and objectives
- Methods: protocol, eligibility criteria, analytic framework, data sources, search strategy, study selection and extraction process, methods for handling missing data, methods to appraise study quality, summary measures of effect size, rationale for pooling, methods of synthesis
- Results: study selection, list of excluded studies with reasons, appraisal of study quality, qualitative synthesis, meta-analysis if done, tables/figures
- Discussion: summary, strengths/limitations, conclusions, gaps, future research needs
- Report funding sources and conflict of interest

**Standard 5.2: Peer review the draft report**

**Standard 5.3: Publish final report in a manner that ensures public access**