2016 AMCP Foundation P&T Committee Competition Training

Synthesizing the Evidence: Increasing the Certainty of Evidence Evaluation

CER Collaborative

AMCP/ISPOR/NPC

AMCP Academy of Managed Care Pharmacy | ISPOR | National Pharmaceutical Council

How to Ask a Question

Raise your hand to ask verbally

Or, type your question in the 'Questions' area

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CER Collaborative – Online Toolkit

- www.cercollaborative.org
  - Sign-up with school name as the organization
  - Use school provided email address and create a unique password
- **Students will provide a copy of their assessment report from the tool and include with competition materials.**

Environmental Context

Staff Needs

- Consolidation
- Transparency
- Maintain Quality and Manage Costs

Information Availability

- Specialty and Diagnostic Products May Have Limited Information
- Increased Availability of High-Quality Data
- Evolution in Research Techniques

CER Collaborative

A Collaboration of the Academy of Managed Care Pharmacy, International Society for Pharmacoeconomics and Outcomes Research and National Pharmaceutical Council

- ***Objective:***
  - Guidance and practical tools to help P&T members critically appraise CER (primarily observational) studies to inform decision making
  - Provide greater uniformity and transparency in the use and evaluation of CER for coverage and decision making

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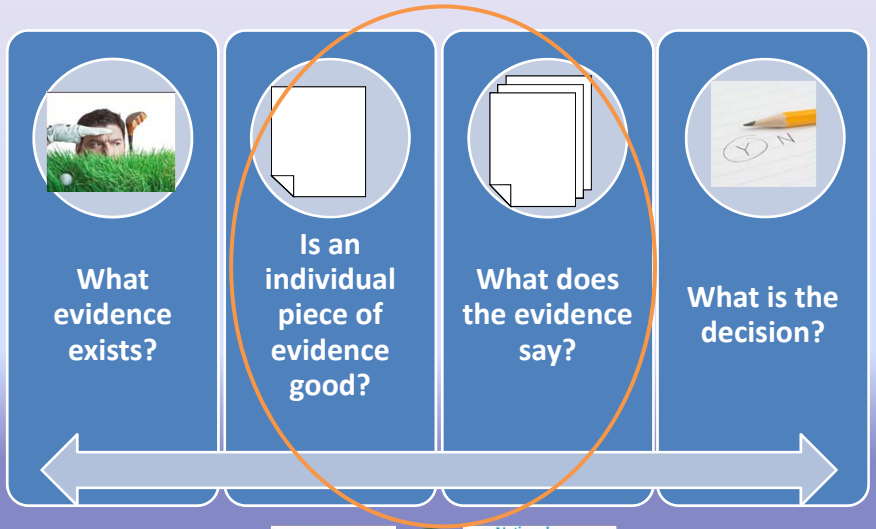
Evidence Synthesis: Part of the Critical Appraisal and Decision Process



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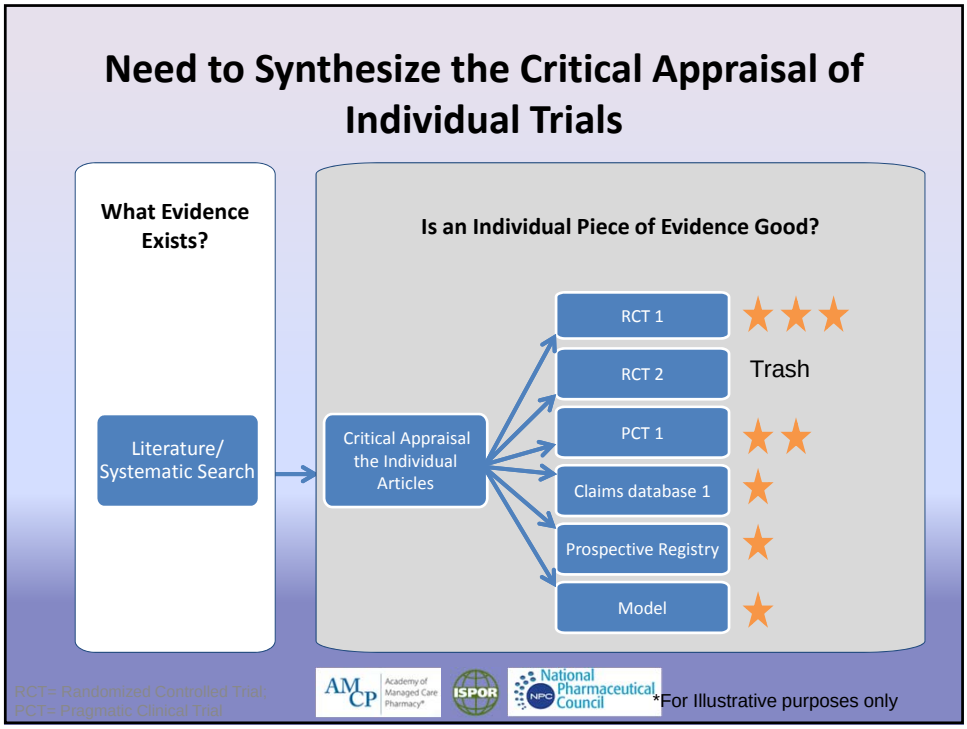
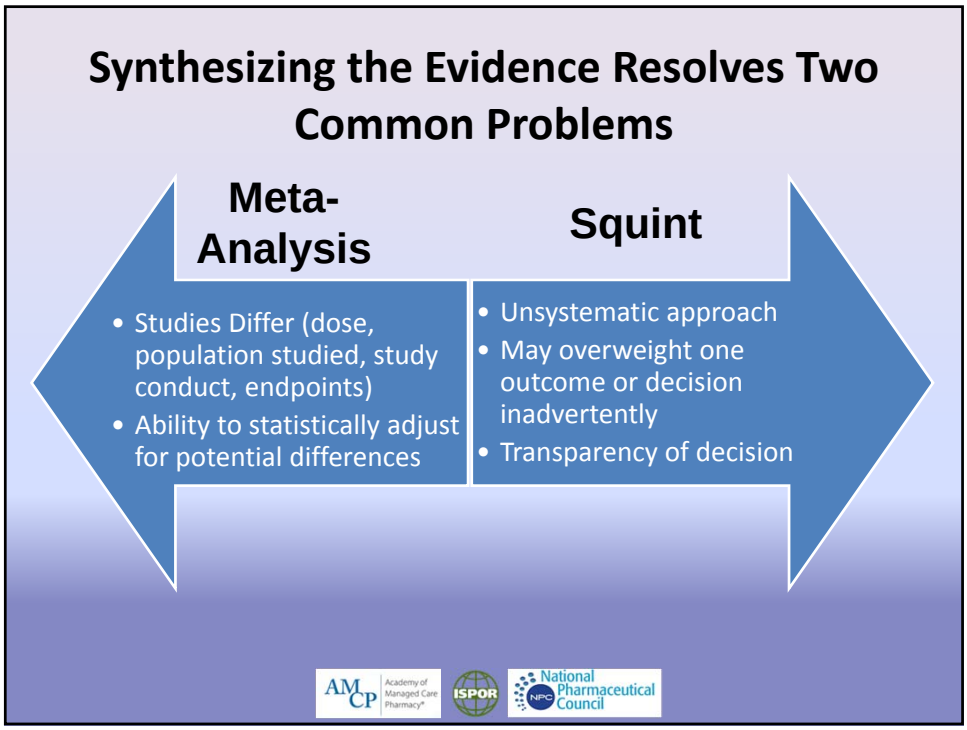
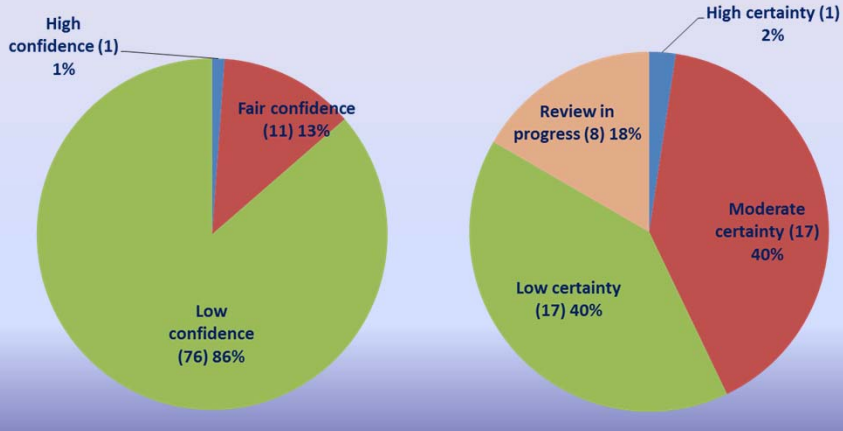

Need to Synthesize the Critical Appraisal of Individual Trials
What Evidence Exists?
Literature/ Systematic Search
Is an Individual Piece of Evidence Good?
Critical Appraisal the Individual Articles
RCT 1
RCT 2
PCT 1
Claims database 1
Prospective Registry
Model
Trash
RCT= Randomized Controlled Trial; PCT= Pragmatic Clinical Trial;
*For Illustrative purposes only

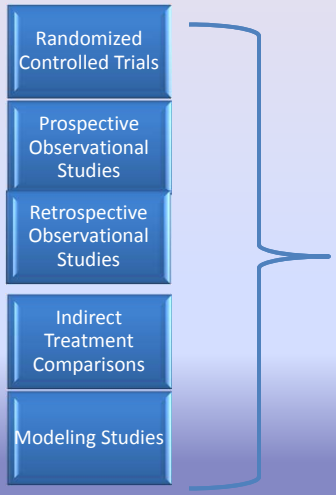

Synthesizing the Evidence Resolves Two Common Problems
Meta-Analysis
Squint
• Studies Differ (dose, population studied, study conduct, endpoints)
• Ability to statistically adjust for potential differences
• Unsystematic approach
• May overweight one outcome or decision inadvertently
• Transparency of decision

Synthesis Evaluation Can Increase Your Decision Confidence



OmedaRx Ratings. CER Collaborative Webinar April 3, 2014

Part 2: Synthesizing A Body of Evidence



Goals:

- **Objectivity**
- **Transparency**
- **Reliability/validity**
- **Ease of application**
- **Experience in P&T decision making**

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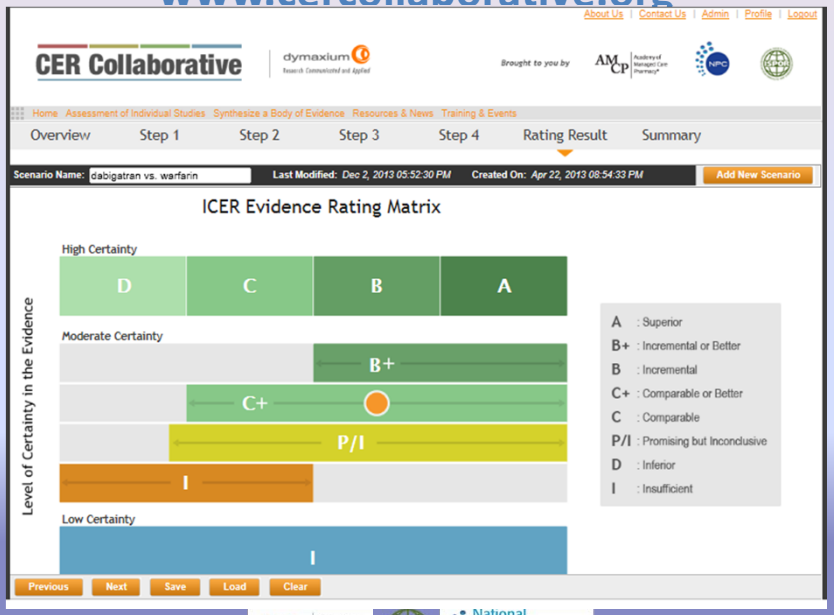
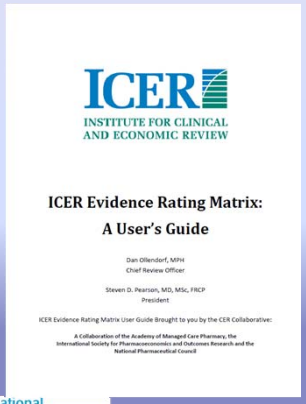


Four Steps to Synthesize Evidence

Steps

1. Determine What You Will Evaluate
2. Identify the Comparative Net Health Benefit
3. Determine the Level of Certainty
4. Confirm the Joint Evidence Rating

User's guide



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Step 1. Determine What You Will Evaluate: PICO(TS)

- **P= Population**
- **I = Intervention(s) of interest**
- **C= Comparator intervention(s)**
  - May be active or standard of care
- **O= Key Outcomes**

Optional:

- **T= Time Horizon**
- **S= Setting of Interest**

Step 2. Identify the Magnitude of Comparative Net Health Benefit

- **The comparison may be vs. placebo or active comparator**
- **Evaluate the evidence on benefits (clinical, patient oriented, etc.) for both treatments**
- **Evaluate the evidence on risks (safety) for both treatments**
- **Weigh the *comparative* balance of evidence on benefits and harms**

Step 2. Identify the Magnitude of Comparative Net Health Benefit

- **Select and justify -- a "point estimate" for the best estimate of comparative net health benefit in one of the following categories:**
  - ***Negative***
    - ***aspirin vs. warfarin for stroke prevention in mod-high risk patients***
  - ***Comparable***
    - ***ACE inhibitors vs. ARBs for long-term control of hypertension***
  - ***Small***
    - ***TPA vs. streptokinase for myocardial infarction***
  - ***Substantial***
    - ***Imatinib vs. interferon in chronic myelogenous leukemia***

Step 3. Determine the Level of Certainty

- **Limitations in a Body of Evidence:**
  1. **Amount** of evidence
  2. **Potential bias** due to the design and conduct of included studies
  3. **Directness**
     - Of the measured outcomes (e.g. surrogate outcomes) to patient-centered outcomes
     - Of the comparison possible: head-to-head studies vs. indirect comparisons
  4. **Duration** of studies given the time needed to capture important benefits and harms
  5. **Precision** of results
  6. **Consistency** of results
  7. **Applicability** of results (i.e., generalizability to the "real world")

Step 3. Determine the Level of Certainty

Low	Medium	High

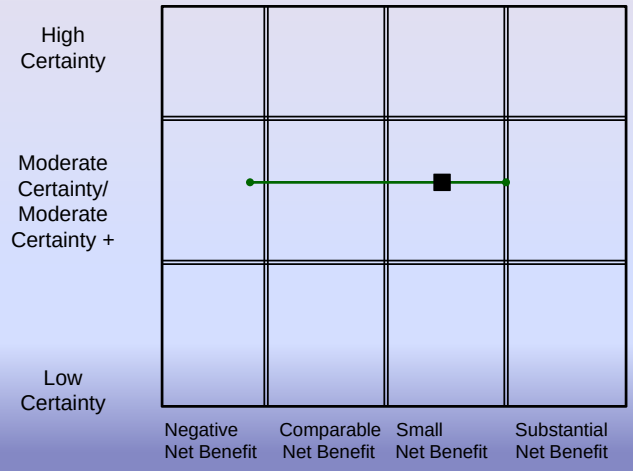
• Mostly poor-quality, smaller studies
• Evidence insufficient to estimate net benefit at all
• Flaws in evidence base make it impossible to determine if intervention inferior, comparable, or superior to comparator
• *High likelihood that new evidence would substantially change conclusions regarding net benefit*
	• Mix of study quality
	• Cannot estimate net benefit with good precision, based on limitations including:
	  • Weak study design
	  • Inconsistent findings
	  • Indirect evidence only
	  • Limited applicability
	  • Evidence of reporting bias
	• *Future studies may result in modest shifts in estimates of net health benefit*
		•
		• Mostly high-quality, larger studies
		• Conducted in representative patient populations
		• Direct comparisons available
		• Address important outcomes or validated surrogate outcomes
		• Long-term data on benefits/risks available
		• Consistent results
		• *Future studies unlikely to change conclusions*

Step 3. Determine the Level of Certainty

An Alternate approach:

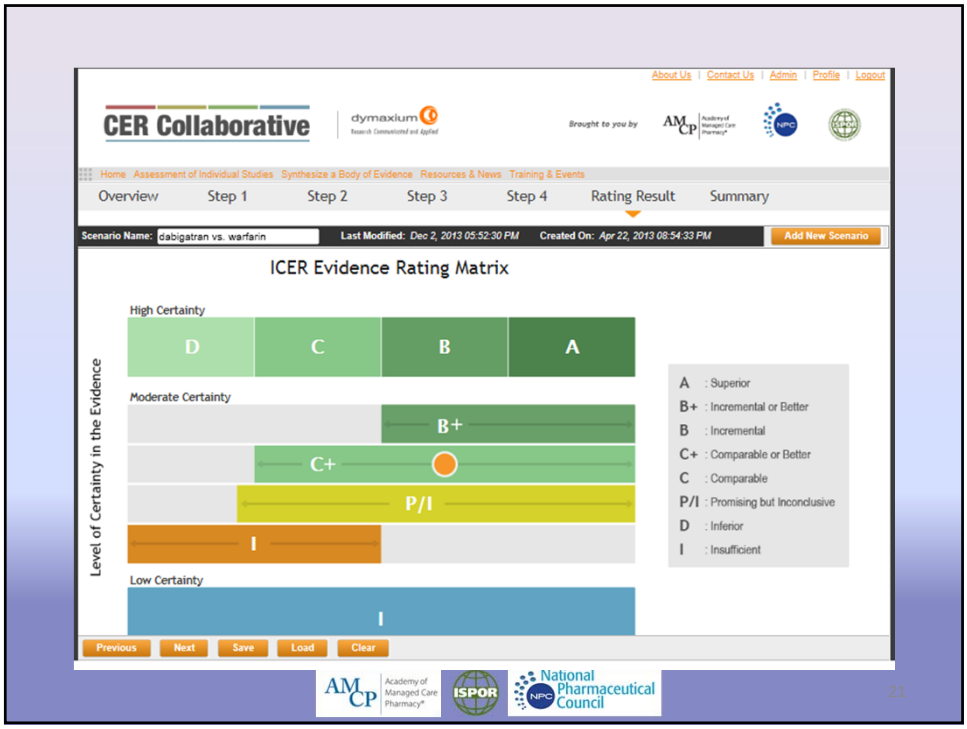
- ***High*:**
  - Confidence interval limited to 1 category of comparative net benefit
- ***Moderate:***
  - Confidence interval extends for 2-3 categories on the matrix
  - Is there a chance that it has a negative benefit?
- ***Low:***
  - Confidence interval extends across all 4 categories on the matrix
  - Evidence is inadequate to frame a reasonable estimate of comparative net benefit

ICER Evidence Rating Matrix



Step 4. The Joint Rating

- **High certainty- allows a precise rating category**
  - A = superior
  - B = incremental
  - C = comparable
  - D = inferior
- **Moderate certainty- reasonable chance that the true net benefit may change**
  - B+ = Incremental or Better
  - C+= Comparable or Better
  - P/I = “promising but inconclusive”
- **Low certainty in any point estimate**
  - I = insufficient



Guidance for Using the Matrix

- **Multiple endpoints can make it hard to judge the balance of risks and benefits**
  - Options:
    - Mathematical equations (NNT or NNH) or Quantitative measures (QALYs)
    - Internal discussion/consensus with your team
- **Which limitations are most important (e.g., how much should the lack of long-term safety data affect the level of certainty)?**
  - Options:
    - Internal discussion/consensus
- **Everything is Insufficient or P/I at best**
  - Often this distinction is most important anyway
  - Internal discussion/consensus

NNT= Number Needed to Treat; NNH= Number Needed to Harm; QALY=Quality adjusted Life Year

Hints for Successful Use in the P&T Competition

- **Synthesize ALL of the evidence (RCTs and non-RCTs) at one time**
- **Consider benefits and risks of the treatments**
- **Justify your answers in a clear but concise manner**
- **Questions- use additional tools**
  - Glossary
  - Synthesis user guide
- **Evidence + contextual factors = decision**

Case Example 1: Dabigatran and Stroke Prevention in Atrial Fibrillation

- **Clinical Question:**
  - What is the net benefit of dabigatran vs. warfarin for stroke prevention in atrial fibrillation
- **PICO**
  - P: Stroke prevention in Atrial Fibrillation
  - I: dabigatran
  - C: warfarin
  - O: Hemorrhagic stoke, total stroke and mortality

Case Example 1:

Study #	Author	Year	Design	Dab	Warf	Dura-tion	Pop'n
1	RE-LY	2009	RCT	6,076	6,022	2yrs	CHADS 2 Score 2.2; AF 67% persistent AF; 33% Paroxysmal; 20% prior stroke or TIA
2	RELY-ABLE	2013	OS, OL Ext	2,937	n/a	1-3 yrs	CHADS2 2.1; 31% persistent AF; 33% paraoxsymal; 21% prior stroke or TIA
3	Steinberg	2013	OS, registry	1,217		1 year	CHADS 2: 2.3 ; 75 year old; 42% Female; 51% paroxysmal ; 8% prior stroke;

Thank you!
Questions?