PICO Questions Outcomes and GRADE

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Objectives

1. More in-depth analysis of PICO question morphology
2. Defining suitable outcomes for PICO questions and rating their importance
Perspective on outcomes

• GRADE is outcome-centric
• Evidence assessment is outcome-specific
• Not all outcomes created equal
• Each outcome should be considered separately
Rules of Thumb

• PICO formulation is a critical step in guideline development
• Essential for focus, target audience, staying on track
• Don’t let the tail wag the dog
<table>
<thead>
<tr>
<th>Step</th>
<th>Question &amp; Description</th>
<th>References</th>
<th>Feedback</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Establish methods for generating the questions for the guideline, prioritizing questions, and selecting and ranking outcomes.</td>
<td>3-7.9.11-16, 19,20,23,24, 30,34,40,44, 46,47,53</td>
<td>JCE GRADE Guidelines: Framing the Question and Deciding on Important Outcomes, AWMF Rules for Guidelines: Formulating Clinically Relevant Questions (in German; see AWMF Manual pg. 17 for English)</td>
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<td>2.</td>
<td>Generate and document the key questions (e.g. clinical, health, policy, cost-effectiveness) to be answered in the guideline using a standard format (e.g. PICO) and determine the criteria by which the questions generated will be prioritized if it is not feasible to answer all questions (e.g. survey guideline panel members, survey stakeholders).</td>
<td>3-7.9-16,19, 20,23,24,27, 30,34,40,44, 46,47,53</td>
<td>PICO Framework (Population, Intervention, Comparator, Outcome)</td>
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<td>3.</td>
<td>Explicitly describe the population to whom the guideline is meant to apply. Take into consideration specific characteristics of the population, such as prevalence of multiple comorbidities in the population, geographical setting, and equity issues (e.g. plausible reasons for anticipating differential relative effects across disadvantaged and advantaged populations).</td>
<td>4-9.11,12,14-16, 19,20,23,24, 27,31,35,40, 42,44,54,55</td>
<td>PATS: How to Integrate Multiple Comorbidities in Guideline Development, Dutch Knowledge Base for Guideline Development: Tool for developing population-specific recommendations, Dutch Knowledge Base for Guideline Development: Tool for considering sex differences in guideline development</td>
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Welcome

The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it. » learn more
GRADE guidelines: 2. Framing the question and deciding on important outcomes

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Good Questions = Good Recommendations

• There is controversy / doubt around the answer
• Want to confirm the present answer
• Has a chance of being answered, or will determine research in future
• Will improve care, cost, quality of life
PICO

- Four clinical domains (Rx, Dx, Prog, Harm)
- Patient / Population
- Intervention (passage of time in prognosis)
- Comparison (Crit std in Dx)
- Outcome
How to select outcomes

- Be comprehensive
- Think outside the literature
- Patient / clinician / public input
- Safety considerations (often under-reported)
- Patient-important
**Systematic review**

- Formulate question
- Select outcomes
- Rate importance
- Outcomes across studies
- Create evidence profile with GRADEpro
- Rate quality of evidence for each outcome

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<th>P</th>
<th>I</th>
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<tbody>
<tr>
<td>Outcome</td>
<td>Critical</td>
<td>Outcome</td>
<td>Critical</td>
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<tr>
<td>Outcome</td>
<td>Important</td>
<td>Outcome</td>
<td>Not important</td>
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Summary of findings & estimate of effect for each outcome

**Guideline development**

Formulate recommendations:
- For or against (direction)
- Strong or weak (strength)

By considering:
- Quality of evidence
- Balance benefits/harms
- Values and preferences

Revise if necessary by considering:
- Resource use (cost)

Rate overall quality of evidence across outcomes based on lowest quality of *critical* outcomes

- “We recommend using...”
- “We suggest using...”
- “We recommend against using...”
- “We suggest against using...”

<table>
<thead>
<tr>
<th>RCT start high, obs. data start low</th>
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<tbody>
<tr>
<td>Grade up</td>
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<td>Grade down</td>
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<tr>
<td>1. Risk of bias</td>
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<td>2. Inconsistency</td>
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<td>3. Indirectness</td>
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<td>4. Imprecision</td>
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<td>5. Publication bias</td>
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<td>1. Large effect</td>
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<td>2. Dose response</td>
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<td>3. Confounders</td>
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Prioritizing outcomes

- Critical i.e. critical for decision-making
- Important – for decision-making but not critical
- Less important
- Process should be importance-driven and not evidence-driven
Methodological considerations

• Generate a list of outcomes (from literature, from the panel, from clinical experts, from patient groups)

• Ask panel to rank the outcomes by importance (anonymous)
Methodological considerations

- Calculate the mean or median rating for each outcome (between 1-9)
- Identify outcomes with large variability in rating, discuss these with panel
- Obtain agreement on ranking of outcomes
- Critical and important outcomes are included
1. OUTCOMES FOR TREATMENT OPTIONS (cold knife conization, cryotherapy and LEEP)

Choose the most important outcomes for decision making: Consider outcomes that might be important to someone making a decision to use or not to use the treatment (make sure to rank benefits and adverse effects).

Rate the relative importance of each outcome on a 9 point scale ranging from 1 (not important) to 9 (critical). You can use the same rating several times (i.e. same number for more than one outcome).

1 – 3 not important,
4 – 6 important, but not critical for making a decision
7 – 9 critical for making a decision

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<tr>
<th>Outcome</th>
<th>1 (not important)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9 (critical)</th>
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<tr>
<td>Residual/recurrent CIN 2,3 (after 6, 12 months and 24 months)</td>
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<td>HPV negative (after 6, 12 and 24 months)</td>
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<td>Pelvic Inflammatory Disease</td>
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<td>Major infections <em>(requiring hospital admission and antibiotics)</em></td>
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<td>Premature delivery</td>
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<td>Infertility</td>
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<td>Maternal death</td>
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<td>Fetal/neonatal spontaneous abortions</td>
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<td>Major Bleeding <em>(requires hospitalization/blood transfusion)</em></td>
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<td>Minor bleeding <em>(requires packing or suturing)</em></td>
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<td>Damage to other organs/other surgery required – such as injury to bladder or urethra</td>
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Comments or other outcomes (indicate not important, important, critical)
Importance of outcomes

9  Mortality
8  Myocardial infarction
7  Fractures
6  Pain due to soft tissue calcification / function
5
4
3
2  Flatulence
1

Surrogates: relation to important outcomes increasingly uncertain

Critical for decision making

Important, but not critical for decision making

Low importance for decision making

Coronary calcification → Ca^{2+}/P-product
Bone density → Ca^{2+}/P-product
Soft tissue calcification → Ca^{2+}/P-product
Why prioritize outcomes

• Focuses search and evidence review / synthesis
• Defines the elements of the Evidence Profile and SoF table
• QoE for critical outcomes defines the QoE for the entire PICO-related evidence base
Summary

• Outcomes are at the core of the GRADE approach
• Select them wisely
• Define early
• Anchor for next steps
• Not carved in stone – can be revisited