Outcomes and GRADE

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Perspective on outcomes

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

Gordon H. Guyatt, Andrew D. Oxman, Regina Kunz, David Atkins, Jan Brozek, Gunn Vist, Philip Alderson, Paul Glasziou, Yngve Falck-Ytter and Holger J. Schünemann

Journal of Clinical Epidemiology
Volume 64, Issue 4, Pages 395-400 (April 2011)
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**

**PICO**
- Outcome: Critical
- Outcome: Critical
- Outcome: Important
- Outcome: Not important

**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…”
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

<table>
<thead>
<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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<tbody>
<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 (requiring hospital admission and antibiotics)</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 (requires hospitalization/blood transfusion)</td>
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<td>Minor bleeding (requires packing or suturing)</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.

Critical for decision making

Important, but not critical for decision making

Low importance for decision making

Surrogates: relation to important outcomes increasingly uncertain

- Coronary calcification
- Bone density
- 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
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies), Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Effects</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>1,196 (1 study), 6 or 12 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 0.49 (0.04-5.4)</td>
<td>3 per 1,000</td>
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<td>2 fewer per 1,000 (from 3 fewer to 15 more)</td>
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<td>Recurrent VTE</td>
<td>1,196 (1 study), 6 or 12 mo</td>
<td>High</td>
<td>HR 0.18 (0.09-0.39)</td>
<td>71 per 1,000</td>
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<td>58 fewer per 1,000 (from 43 fewer to 64 fewer)</td>
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<tr>
<td>Major bleeding</td>
<td>1,188 (1 study), 6 or 12 mo</td>
<td>Moderate due to imprecision</td>
<td>RR 4.9 (0.58-42)</td>
<td>i</td>
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<td>7 more per 1,000 (from 3 more to 16 more)</td>
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Health Care Question (PICO)
Systematic reviews

Studies

Outcomes

Important outcomes

Critical outcomes

Generate an estimate of effect for each outcome

Rate the quality of evidence for each outcome, across studies
RCTs start high, observational studies start low

(-)
Study limitations
Imprecision
Inconsistency of results
Indirectness of evidence
Publication bias likely

(+)
Large magnitude of effect
Dose response
Plausible confounders would ↓ effect when an effect is present or ↑ effect if effect is absent

Final rating of quality for each outcome: high, moderate, low, or very low

Rate overall quality of evidence
(lowest quality among critical outcomes)

Decide on the direction (for/against) and grade strength (strong/weak*) of the recommendation considering:
Quality of the evidence
Balance of desirable/undesirable outcomes
Values and preferences

Decide if any revision of direction or strength is necessary considering: Resource use

*also labeled “conditional” or “discretionary”
Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Anthony J. Comerota, MD; Paolo Prandoni, MD, PhD; Henri Bounnameaux, MD; Samuel Z. Goldhaber, MD, FCCP; Michael E. Nelson, MD, FCCP; Philip S. Wells, MD; Michael K. Gould, MD, FCCP; Francesco D'Antoni, MD; Mark Crowther, MD; and Susan R. Kahn, MD

- Burden of anticoagulation (testing / cost / interactions)
- Quality of life (NOAC vs VKA)
- Included as outcome despite absent data
Summary

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