Using the GRADE approach for Guideline Development

A step-by-step guide

Thomy Tonia MSc, ERS Methodologist
Before starting....

• Define the scope of the Guideline
• Form Guideline panel
• Declare conflicts of interest and ways they will be dealt with
Remember!

- If you aim to make recommendations for clinical practice, you need to inform them via a systematic review and grading of the evidence and degree of the recommendations (i.e. use the GRADE approach)
Step 1: Formulate the questions

- Use the PICO format

**Population**  
In patients hospitalized for COPD exacerbations

**Intervention**  
is initial treatment with IV corticosteroids

**Comparison**  
compared to oral corticosteroids

**Outcome**  
better (e.g. reduction in length of hospital stay)?
Step 1: Formulate the questions

• Restrict the number of questions (about 7)
• Each PICO question will result in one recommendation
• No PICO question, no recommendation!
Step 2: Select outcomes of interest

• Select outcomes for each PICO question *before* conducting the literature review
• Outcomes should be importance driven and not evidence driven
• Select outcomes that are important to patients and important for guiding clinicians
• Avoid surrogate outcomes (for example biomarkers)
Step 2: Rate outcome importance

- Rate the importance of the selected outcomes *before* conducting the literature review
- How important is each outcome for decision making? Not important, important, of critical importance
- Suggested rating scale:
Step 3: Systematic Review

• Pragmatic literature search
  - Search for recent, well-conducted systematic reviews and build up on them
    - Search main database(s) only
    - One assessor
Step 3: Systematic Review

• Select studies according to predefined criteria

• Extract outcomes of interest

• Meta-analyse, when applicable
Step 4: GRADE the evidence

• Create evidence tables for each PICO question
• Evidence tables contain 2 parts: results and quality of evidence
• Quality is evaluated per outcome and not per study
• There are 4 degrees of quality: high, moderate, low and very low
• RCTs start from high quality; observational studies start from low quality
Step 4: GRADE the evidence

• Quality can be decreased (one or two levels per factor) based on the following factors:
  – Risk of bias
  – Indirectness
  – Inconsistency
  – Imprecision
  – Publication bias
Step 4: GRADE the evidence

Risk of bias

• Assess the studies included for each outcome. Factors to consider: concealment of allocation, intention to treat analyses, large loss to follow-up etc)

• Note that a study might have high risk of bias for one outcome and low for another!

• After assessing the risk of bias for each study separately, you have to make a decision on the overall degree of risk of bias for each outcome
Step 4: GRADE the evidence

**Indirectness**

- Indirect comparison (e.g. we want to compare drug A to drug B but have only found studies comparing drug A to placebo and drug B to placebo)

- Differences in population, intervention, comparison, outcomes of interest between the identified studies and the scope of our guideline
Step 4: GRADE the evidence

Inconsistency

• Variability/ heterogeneity of results

• Look for possible reasons

• Look at the similarity of point estimates

• Look at the degree of overlap of CIs

• Statistical criteria ($I^2$ etc)
Step 4: GRADE the evidence

Imprecision

• Estimate of effect includes both appreciable benefits and not appreciable benefits (or even harms)

• Set a threshold for clinical decision making: would your decision to recommend an intervention be different if the lower versus the upper CI represented the true effect estimate?
Step 4: GRADE the evidence

Publication bias

- Failure of reporting studies that were undertaken (often: showing negative effect)
- Difficult to estimate!
- Examine funnel plots
- Higher risk of publication bias when there are only very few small studies available that show positive effect
Step 4: GRADE the evidence

• Quality per outcome (according to the criteria before)

• Quality per question (rule: look at the critical outcomes; what is the lowest quality for a critical outcome; this would be the overall quality for this particular question)
Step 5: Going from evidence to recommendations

• Factors that need to be considered:
  - Quality of evidence
  - Balance between benefits and harms
  - Values and preferences of the patients
  - Costs
Step 5: Going from evidence to recommendations

- Two degrees of recommendations (for or against an intervention):
  - Strong ("We recommend....")
  - Conditional ("We suggest...")

- It is possible to derive strong recommendations from low quality evidence, as quality is only one factor to take into account (see previous slide)
Need more help?

• Please see the separate document in the ERS website with further resources for producing evidence-based guidelines
• Read our FAQs outlined in our website
• Contact the ERS Methodologist, Thomy Tonia at thomy.tonia@ersnet.org