GRADE
Evidence-Based Medicine Methodology
Health Evidence Review Commission

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Statement of Disclosure
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➢ I have no commercial or academic conflicts of interest

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  ➢ Co-Chair: NHLBI Implementation Science Work Group

➢ Member: State of Oregon Health Evidence Review Commission (HERC)
  ➢ Chair: HERC Evidence-Based Guidelines Subcommittee

➢ Member: GRADE Working Group
As one moves to the right there is:
- Decreasing bias in information
- Increasing ability to predict health outcomes with confidence

There will still be a need for pathophysiologic reasoning and expert opinion
Evidence-Based Medicine
In HERC

➢ GRADE Methodology
  ▪ Grading of Recommendations, Assessment, Development and Evaluation
  ▪ International collaboration
  ▪ Rigorous, systematic, transparent approach to grading quality of evidence and strength of recommendations

➢ Clinical efficacy is paramount
  ▪ Patient Oriented Evidence That Matters (POEMs)
  ▪ Cost-effectiveness can be explicitly addressed
What Outcomes & Evidence Matter?

POEMs: Patient Oriented Evidence that Matters
- Addresses a question that patients & doctors encounter
- Measures outcomes that patients care about
  - Symptoms
  - Morbidity
  - Quality of Life
  - Mortality
- Has the potential to change patient & doctor behavior


GRADE Categories of Outcomes
- Critical: 1º factors influencing a recommendation
- Important, but not Critical: 2º factors influencing a recommendation
- Limited Importance: May or may not influence a recommendation
# GRADE: Strength of Recommendation Implications

<table>
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<tr>
<th></th>
<th>Strong</th>
<th>Weak</th>
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### GRADE: Strength of Recommendation
Factors that Inform the Decision

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<tr>
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<td>The more they vary, or the greater the uncertainty, the higher the likelihood that a weak recommendation is warranted</td>
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<tr>
<td>Resource use (Costs)</td>
<td>The higher the costs of an intervention, the lower the likelihood that a strong recommendation is warranted</td>
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GRADE: Balance
Between Desirable and Undesirable Effects

- **Desirable** effects include beneficial health outcomes and less burden
- **Undesirable** effects include harms and more burden
- **Burdens** are the demands of adhering to a recommendation that patients or caregivers (e.g. family) may dislike, such as having to take medication or the inconvenience of going to the doctor’s office
GRADE: Balance

Factors that Inform the Decision

- Importance of Outcomes (to Patients)
  - Stronger recommendations for interventions that increase the probability of beneficial outcomes or decrease the risk of adverse outcomes with high patient importance

- Baseline Risk
  - The higher the baseline risk, the greater the magnitude of benefit and the more likely the recommendation will be strong

- Magnitude of Effect
  - If large relative effects of an intervention consistently point in the same direction (towards benefits or towards harms and burdens) they are likely to lead to a strong recommendation

- Precision of Estimate
  - The more precise are the estimates of the effect of an intervention, the more likely the recommendation will be strong
GRADE: Quality of Evidence

- Reflects confidence in estimates of efficacy
- A systematic review of the evidence is done for each critical/important outcome
- The overall quality of evidence is the combined grade of the quality of evidence across all critical outcomes
  - If the quality differs across critical outcomes, and:
    - Outcomes point in different directions
      - The lowest quality of evidence for any of the critical outcomes determines the overall quality of evidence
    - All outcomes point in the same direction
      - The highest quality of evidence for a critical outcome that by itself would suffice to recommend an intervention determines the overall quality of evidence
# GRADE: Quality of Evidence
## Putting it All Together

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
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<tbody>
<tr>
<td><strong>Starting grade based on study design</strong></td>
<td><strong>Reduce grade</strong></td>
<td><strong>Raise grade</strong></td>
<td><strong>Final grade</strong></td>
</tr>
<tr>
<td><strong>RCT - High</strong></td>
<td><strong>Study quality (risk of bias)</strong></td>
<td><strong>Large magnitude of effect</strong></td>
<td><strong>High</strong></td>
</tr>
<tr>
<td></td>
<td>Serious (-1) or very serious (-2) limitations</td>
<td>Large effect (+1)</td>
<td>Further research unlikely to change confidence in the estimate of effect</td>
</tr>
<tr>
<td></td>
<td><strong>Inconsistency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Important inconsistency (-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Observational – Low</strong></td>
<td><strong>Indirectness</strong></td>
<td><strong>Very large effect (+2)</strong></td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>Quasi-RCT</td>
<td>Some (-1) or major (-2) uncertainty about directness</td>
<td></td>
<td>Further research likely to have an important impact on confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td><strong>Imprecision</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imprecise or sparse data (-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All others – Very Low</strong></td>
<td><strong>Publication bias</strong></td>
<td><strong>Dose response gradient (+1)</strong></td>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>Case reports</td>
<td>High suspicion (-1)</td>
<td></td>
<td>Further research very likely to have an important impact on confidence in the estimate and may change the estimate</td>
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<tr>
<td>Case series</td>
<td></td>
<td><strong>All plausible confounders would have reduced the effect (+1)</strong></td>
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Legend:
- **Weak** (Low) evidence indicates small or uncertain effect
- **Moderate** (Moderate) evidence indicates moderate or certain effect
- **Strong** (High) evidence indicates large or very certain effect
- **Very strong** (Very High) evidence indicates very large or extremely certain effect
Uncertainty concerning values and preferences or their variability among patients may lower the strength of a recommendation.

- While it is ideal for clinicians to elicit patient preferences and values directly from patients or to obtain values and preference estimates from population based studies, such studies are often unavailable.
- There is some systematic research of values and preferences, and guideline panel members' experience with patients provides additional insight.

When value or preference judgments are particularly important for the interpretation of recommendations, authors should describe the key values they have attributed in making a recommendation.
May legitimately choose to leave considerations of resource use aside
- But be explicit about the decision
First decide on the quality of evidence regarding other outcomes, before addressing cost
- Resource use usually becomes important when advantages and disadvantages are closely balanced
Offer only a single recommendation
- Refrain from issue two recommendations, one not taking resource use into account, and a second doing so
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Emerging Construct: Rationale Table
(For Information Only)

- Concise description of key elements behind a recommendation
- Basis of Recommendation Statement
  - Describes how the 4 GRADE domains of strength of recommendation were utilized to derive the final recommendation and its strength
    - Example: “Despite the lack of direct evidence that demonstrates that rescreening is beneficial, we believe that clinicians and patients are likely to place a high value on the potential, but unproven, benefit of rescreening. Therefore, we conclude that rescreening for low Bone Mineral Density with DXA is an option and we have suggested rescreening intervals based on the patient’s initial T-score.”
- Four GRADE Domains of Strength of Recommendation
  - Brief, high-level overview
  - Hyperlinks to underlying Systematic Review(s)
Main Modifications of GRADE: HERC Processes

- External SRs & CPGs commonly used
  - Outcomes examined are subject to external sources
  - Evidence-grading is subject to external sources
  - Summary of Findings tables for Critical/Important outcomes are subject to external sources

- Values & Preferences less directly addressed

- Exploration of Resource Allocation subject to external sources

- More explicit consideration of policy context

- Adapted for the development of Coverage Guidance
  - GRADE Framework is designed for clinical recommendations
HERC Guidance Development Framework

Refer to HERC Guidance Development Framework Principles for additional considerations

1. Level of Evidence
   - Sufficient
   - Insufficient or Mixed

A. Effectiveness compared to alt. treatment(s) (clinically significant improvement in outcomes)
   - More effective
     - Treatment risk compared to alt. treatment(s)
       - More
         - Do not recommend (weak)
         - Recommend (strong)
       - Similar or less
         - Do not recommend (strong)
         - Recommend (strong)
   - Similar effectiveness
     - Treatment risk compared to alt. treatment(s)
       - More
         - Do not recommend (strong)
         - Recommend (strong)
       - Similar or less
         - Do not recommend (strong)
         - Recommend (strong)
   - Less effective
     - Treatment risk compared to alt. treatment(s)
       - More
         - Do not recommend (strong)
         - Recommend (strong)
       - Similar or less
         - Do not recommend (strong)
         - Recommend (strong)

B. No alt. treatment(s) available/accessible
   - Effective
     - Treatment risk compared to alt. treatment(s)
       - More
         - Do not recommend (strong)
         - Recommend (strong)
       - Similar or less
         - Do not recommend (strong)
         - Recommend (strong)
   - Ineffective or harm exceeds benefit
     - Treatment risk compared to alt. treatment(s)
       - More
         - Do not recommend (strong)
         - Recommend (strong)
       - Similar or less
         - Do not recommend (strong)
         - Recommend (strong)

Decision Point Priorities
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Alternative effective treatment(s) available/accessible

A. Yes
   - Treatment risk compared to alt. treatment(s)
     - Less
       - Do not recommend (strong)
       - Recommend (weak)
     - More or similar
       - Do not recommend (weak)
       - Recommend (strong)
     - Similar or less
       - Do not recommend (weak)
       - Recommend (strong)
   - Treatment is prevalent
     - Cost
       - Do not recommend (strong)
       - Recommend (weak)
       - Similar or less
       - Do not recommend (weak)
       - Recommend (strong)

B. No
   - Treatment risk compared to no treatment
     - More
       - Do not recommend (weak)
       - Recommend (strong)
     - Similar or less
       - Do not recommend (weak)
       - Recommend (strong)

Clinical research study is reasonable

1. Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability, or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

FINAL 2/18/2013
This framework is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format.

While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.
HERC Guidance Development Framework

Potential Variations From Algorithm Due to Nuances
Emerging GRADE Framework: Coverage Guidance (For Information Only)

Additional elements:

- Is the cost small, relative to the net benefits?
- Is the total cost (impact on budget) low?
- What would be the impact on health inequities?
- Is inappropriate use likely to be an important problem?

GRADE Recommendations for coverage:

- Do not cover
  - Undesirable consequences clearly outweigh desirable consequences
- Coverage, with evidence development
  - Undesirable consequences probably outweigh desirable consequences
- Restricted coverage
  - Desirable/undesirable consequences closely balanced or uncertain
- Cover, with price reduction
  - Desirable consequences probably outweigh undesirable consequences
- Cover
  - Desirable consequences clearly outweigh undesirable consequences
GRADE EBM Methodology

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