The GRADE approach: an emerging consensus to develop guidelines

Putting Science into Standards: evidence-based quality assurance – an example for breast cancer

JRC ISPRA, 20th October 2015
Disclosure statement

• I work at a Cochrane center
• Member of the GRADE working group
• Our group in Barcelona will review evidence for the ECIBC project

• No direct financial COI
What is GRADE?

- Multidisciplinary international working group (> 500 members)
  - Developed a common system to:
    - Rating the quality of the evidence
    - Grading the strength of recommendations
  - Overcome limitations of previous rating systems
    - Explicit and structured

- Grading of Recommendations Assessment, Development and Evaluation (www.gradeworkinggroup.org)
**Systematic review (SR-CPGs)**

1. **Formulate question**
2. **Select outcomes**
3. **Rate importance**
4. **Outcomes across studies**
5. **Create evidence profile with GRADEpro**
6. **Rate quality of evidence for each outcome**

**Randomization increases initial quality**
1. **Risk of bias**
2. **Inconsistency**
3. **Indirectness**
4. **Imprecision**
5. **Publication bias**

- **Grade down**
- **Grade up**

**Summary of findings & estimate of effect for each outcome**

**High**
- **Moderate**
- **Low**
- **Very low**

**Evidence to recommendation (GPCs)**

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

**By considering the following factors:**
- Problem
- Balance benefits/harms
- Resource use
- Equity
- Acceptability
- Feasibility

**Strong vs conditional recommendations**
- “We recommend using...”
- “We suggest using...”
- “We recommend against using...”
- “We suggest against using...”

**Overall quality of evidence across outcomes**
**Quality of the evidence:** The quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation.
**Strength of recommendation:** confidence the panel has in that the desirable effects of adherence to the recommendation outweigh the undesirable effects (or vice versa)

**Evidence to recommendation (GPCs)**

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

*By considering the following factors:*
- Problem
- Balance benefits/harms
- Resource use
- Equity
- Acceptability
- Feasibility

**Strong vs conditional recommendations**
- “We recommend using...”
- “We suggest using...”
- “We recommend against using...”
- “We suggest against using...”

**Overall quality of evidence across outcomes**
## Implications of strong/conditional recommendations

<table>
<thead>
<tr>
<th></th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Most people would want the recommended course of action and <strong>only a small proportion would not</strong></td>
<td>The majority of people would want the recommended course of action, <strong>but many would not</strong></td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td><strong>Most patients should receive the recommended course of action</strong></td>
<td>Be prepared to <strong>help patients to make a decision that is consistent with their values</strong></td>
</tr>
<tr>
<td><strong>Policy makers</strong></td>
<td>The recommendation could be <strong>adapted as a policy in most situations</strong></td>
<td>There is a need for substantial debate and involvement of stakeholders</td>
</tr>
</tbody>
</table>
**A1.3 Is buprenorphine effective for the treatment of opioid dependence?**

**GRADE evidence profile**

**Author(s):** Amato L, Minozzi S  
**Date:** 23 May 2006  
**Question:** Should buprenorphine maintenance versus placebo be used for opioid addiction?  
**Patient or population:** Opioid dependent  
**Settings:** Outpatient and inpatient  
**Systematic review:** Mattick RP et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (2008, in press) [118].

### Quality assessment

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized trials</td>
<td>No limitations</td>
<td>No important inconsistency</td>
<td>One inpatient study (−1)</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retention in treatment: 2–4 mg buprenorphine versus placebo or 1 mg buprenorphine (objective follow-up: 2–16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>141/242 (58%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphine positive urines: 2–4 mg buprenorphine versus placebo or 1 mg buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>242</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retention in treatment: 8 mg buprenorphine versus placebo or 1 mg buprenorphine (objective follow-up: 2–16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>119/218 (54%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphine positive urines: 8 mg buprenorphine versus placebo or 1 mg buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>218</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retention in treatment: 16 mg buprenorphine versus 1 mg buprenorphine (objective follow-up: 2–16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>110/181 (61%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Morphine positive urines: 16 mg buprenorphine versus placebo or 1 mg buprenorphine</th>
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<tr>
<td>No of patients</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>181</td>
</tr>
</tbody>
</table>
Summary of findings:

Compression stockings compared with no compression stockings for people taking long flights

Patients or population: Anyone taking a long flight (lasting more than 6 hours)
Settings: International air travel
Intervention: Compression stockings
Comparison: Without stockings

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic deep vein thrombosis (DVT)</td>
<td>See comment</td>
<td>Not estimable</td>
<td>2821 (9 studies)</td>
<td>See comment</td>
<td>0 participants developed symptomatic DVT in these studies.</td>
</tr>
<tr>
<td>Symptom-less deep vein thrombosis</td>
<td>Low risk population ²</td>
<td>RR 0.10 (0.04 to 0.26)</td>
<td>2637 (9 studies)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 per 1000 (0 to 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk population ²</td>
<td>30 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 per 1000 (1 to 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial vein thrombosis</td>
<td>10 per 1000</td>
<td>RR 0.45 (0.1 to 0.9)</td>
<td>4894</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Developing and evaluating communication strategies to support informed decisions and practice based on evidence (DECIDE): protocol and preliminary results

Shaun Treweek¹, Andrew D Oxman², Philip Alderson³, Patrick M Bossuyt⁴, Linn Brandt², Jan Brožek⁵, Marina Davoli⁶, Signe Flottorp², Robin Harbour⁷, Suzanne Hill⁸, Alessandro Liberati⁹, Helena Liira¹⁰, Holger J Schünemann⁵¹¹, Sarah Rosenbaum², Judith Thornton³, Per Olav Vandvik², Pablo Alonso-Coello¹² and the DECIDE Consortium
DECIDE

• Target groups
  – Clinicians
  – Patients and the public
  – Policy makers

• Multilayered, electronic, web-based, responsive and interactive

• Presentation formats
  – Recommendation
  – Decision aids linked to CPGs
  – Interactive summary of findings (iSoF) tables
  – Interactive evidence to decisions (iEtD) frameworks
  – Online software to develop guidelines (GDT)
## Choice of oral anticoagulation

**Weak recommendation**

It is less clear whether the benefits outweigh the drawbacks. We believe there will be variation in patients' preferences.

We suggest treatment with dabigatran, rivaroxaban or apixaban rather than warfarin.

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### Benefits and harms

**New oral anticoagulants versus warfarin per 1,000 patients treated for 1 year:**

**Death and stroke:** No significant difference  
**Major bleeding:** Overall no relevant difference, but the number of intracranial bleeds was halved with dabigatran, resulting in an absolute risk reduction of 2 fewer per 1000 patients  
**Myocardial infarction:** No significant difference. The exception is dabigatran, which increased the risk compared to warfarin. The absolute risk, however, is generally very low: 5/1000 with warfarin, 6/1000 with dabigatran.  
**Treatment discontinuation (e.g. due to side effects):** 31 interrupted with warfarin, 39 with NOAC.  
**Practical consequences:** Daily medication with all. Regular INR controls and dietary restrictions with warfarin.

### Quality of evidence

**Moderate.** The expected effects of NOAC compared with warfarin is taken from a systematic review with heterogeneity, and imprecise results (wide confidence intervals) for death and bleeding. Dabigatran was associated with an increase in myocardial infarction and treatment discontinuation in a reliable subgroup analysis.

### Preference and values

Studies on patient preferences and values have shown that the average patient is prepared to suffer three major bleeds to avoid one stroke. These studies have guided our recommendation. They are however deemed to be of low quality and there was a high degree of heterogeneity in the study population.

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*Title:* Development of a novel multilayered presentation format for clinical practice guidelines

*Author list:* Annette Kristiansen¹², MD; Linn Brandt¹², MD; Pablo Alonso-Coello³, MD, PhD; Thomas Agoritsas⁵, MD; Elie A. Akl⁵⁶, MD, MPH, PhD; Tara Conboy⁷, RGN, BSc, MSc; Mahmoud Elbarbary⁷, MD, MSc, PhD, EDIC; Mazen Ferwana⁷, MD, PhD; Wedad Medani⁷, MSc; Mohammad Hassan Murad⁸, MD, MPH; David Rigau⁴, MD; Sarah Rosenbaum⁹, PhD; Frederick A. Spencer⁴, MD; Shaun Treweek¹⁰, Prof; Gordon Guyatt¹, MD, FCCP; and Per Olav Vandvik¹², MD, PhD.

Decision aids

- Conditional recommendations -> Shared decision making
  - Linking DAs and GRADE guidelines
  - Semiautomated production (evidence profiles)
  - For the clinical encounter
iSoF
The key information you need to understand the benefits and harms of treatments

Learn more about iSoF tables
Browse
Explore an example

isof.epistemonikos.org
Who is it for?

Guideline panels
Policy makers
Researchers
Health professionals
Special interest groups
Journalists
Patients and public
### Antibiotics for middle ear infection (acute otitis media) in children

#### Study characteristics
- **Participants:** Children with middle ear infection
- **Intervention:** Antibiotics plus paracetamol (e.g., Calpol) or other pain relief, as needed
- **Comparison:** Placebo plus paracetamol (e.g., Calpol) or other pain relief, as needed

#### Source:
Two reviews: a Cochrane review, and another systematic review

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Plain language statements</th>
<th>Absolute Effect</th>
<th>Relative effect</th>
<th>Certainty of the evidence</th>
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<tr>
<td>Pain or fever after 3 to 7 days</td>
<td>After 3 to 7 days antibiotics probably slightly reduce the number of children who have pain or fever compared to no antibiotic treatment</td>
<td><strong>26</strong> per 100</td>
<td><strong>24</strong> per 100</td>
<td>RR 0.92 (0.85 to 1.01)</td>
</tr>
<tr>
<td></td>
<td>RR 0.92 (0.85 to 1.01) Based on data from 1643 children in 6 studies</td>
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<td>Diarrhoea, vomiting, or rash</td>
<td>Antibiotics increase the number of children who have diarrhoea, vomiting, or rash compared to no antibiotic treatment</td>
<td><strong>20</strong> per 100</td>
<td><strong>27</strong> per 100</td>
<td>RR 1.38 (1.19 to 1.59)</td>
</tr>
<tr>
<td></td>
<td>RR 1.38 (1.19 to 1.59) Based on data from 2107 children in 8 studies</td>
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<td></td>
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<td><strong>Pain or fever after 3 to 7 days</strong></td>
<td>After 3 to 7 days antibiotics probably slightly reduce the number of children who have pain or fever compared to no antibiotic treatment</td>
<td><strong>With Placebo</strong>&lt;br&gt;26 out of 100 children would still have pain or fever after 3 to 7 days and 74 would not.</td>
<td><strong>With Antibiotics</strong>&lt;br&gt;24 out of 100 children would still have pain or fever after 3 to 7 days and 76 would not.</td>
<td><strong>RR 0.92 (0.85 to 1.01)</strong>&lt;br&gt;Based on data from 1643 children in 6 studies</td>
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**Read on**
## Antibiotics for middle ear infection (acute otitis media) in children

### Outcomes

#### Pain or fever after 3 to 7 days
- **With Placebo:** 26 out of 100 children would still have pain or fever after 3 to 7 days and 74 would not.
- **With Antibiotics:** 24 out of 100 children would still have pain or fever after 3 to 7 days and 76 would not.

Differences in outcomes:
- **Favours Antibiotics:** 2 less per 100 children
- **Favours Placebo:**

#### Diarrhoea, vomiting, or rash
- **With Placebo:** 20 per 100
- **With Antibiotics:** 27 per 100

Difference: 7 more per 100 children (85% CI: 3 to 11 more per 100 children)

#### Possible hearing problems after 3 months
- **With Placebo:** 24 per 100
- **With Antibiotics:** 23 per 100

Difference: 1 less per 100 children (95% CI: 6 less to 6 more per 100 children)

### Certainty of the evidence

- Pain or fever: Moderate
- Diarrhoea, vomiting, or rash: High
- Possible hearing problems: Low
iEtD

interactive Evidence to Decision frameworks

Introduction to the iEtD
Guidance
Feedback form
Information for organisations who want to use the iEtD

EXPLORE AN EXAMPLE

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement n° 285583

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ietd.epistemonikos.org
A tool for panels or groups making of decisions or recommendations

• Clinical recommendations
• Decisions about diagnostic tests
• Coverage decisions
• Health system and public health recommendations and decisions
Purpose of framework:

To help guideline panels and decision makers move from evidence to a recommendation or decision by:

• Informing judgements about the **pros and cons** of each option that is considered
• Ensuring that **all important factors** that determine a decision are considered in a balanced way
• Providing a concise **summary of the best available research evidence** to inform judgements about each criterion
• Helping to **structure discussion** and identify reasons for disagreements
• Making the basis for a decision **transparent** to those affected
Other uses

- Panels adapting a recommendation to make a decision about it for their own setting
  - Reduce duplication of efforts
  - Database of Evidence Profiles – iEtD frameworks
- People who are affected by a decision and who want to know what evidence and judgments underly it
**Question**

**Question details**

Patients: Patients with atrial fibrillation and a moderate to high risk of stroke who are currently taking warfarin

Intervention: Dabigatran (150 mg) daily

Comparison: Warfarin

Main outcomes: Death, Stroke, Major bleeding, Myocardial infarction, Treatment burden

Setting: High-income country
### Desirable effects

**How substantial are the desirable anticipated effects?**

### Undesirable effects

**How substantial are the undesirable anticipated effects?**

#### Research evidence

**Summary of findings:** *Bedaquiline for multidrug-resistant tuberculosis* (See an interactive version here)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Absolute Effect</th>
<th>Relative effect</th>
<th>Certainty of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without bedaquiline</td>
<td>With bedaquiline</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Cured by end of study</td>
<td>32 per 100</td>
<td>58 per 100</td>
<td>RR 1.81</td>
</tr>
<tr>
<td>(95% CI: 8 to 42 more per 100 patients)</td>
<td></td>
<td></td>
<td>Based on data from 132 patients in 1 study</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2 per 100</td>
<td>7 per 100</td>
<td>RR 3.6</td>
</tr>
<tr>
<td>(95% CI: 1.7 to 8.2 more per 100 patients)</td>
<td></td>
<td></td>
<td>Based on data from 207</td>
</tr>
</tbody>
</table>
Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

**Overall**

- Extensively drug-resistant tuberculosis (XDR-TB)

**Research evidence**

Modelling of the incremental cost-effectiveness of adding bedaquiline to WHO recommended MDR-TB regimens was conducted by an independent consultant contracted by WHO for review by the expert group. The model assumed that bedaquiline would be added to treatment for all patients starting MDR-TB treatment. Several scenarios were explored to appraise the cost-effectiveness of bedaquiline in these settings. Under the model assumptions, the bedaquiline-containing regimens were assessed as relatively cost-effective in most settings, but results were ambiguous in low-income settings, and highly dependent on the assumptions made about the generalizability of trial results to routine settings.

**Additional considerations**

There are variations of cost effectiveness across settings based on data and assumptions used in the model – that may not reflect real life situations. In addition, there were a series of limitations in the model being used for analysis of cost-effectiveness (e.g., no accounting of serious adverse events, no accounting for effect on transmission, etc.)

As the recommendation of the expert group is to use bedaquiline for only selected sub-groups of the full MDR-TB patient population (as opposed to all patients with MDR-TB that were considered in the cost-effectiveness analysis), the cost-effectiveness model needs to be further refined such that results are available for these sub-groups specifically.

**Judgement**
Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

<table>
<thead>
<tr>
<th>Overall</th>
<th>Extensively drug-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Research evidence
- Additional considerations

Judgement

Voting results

- Don't know
- Varies
- Favours the comparison
- Probably favours the comparison
- Does not favour either
- Probably does not favour the comparison
- Favours the intervention

Detailed judgements

Panel discussion
Cost-effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

- Extensively drug-resistant (XDR) tuberculosis

- Research evidence

- Additional considerations

- Judgement

Voting results

0 = Don't know
1 = Favour the intervention
0 = Favour the comparison
0 = Varies
0 = Does not favour either
0 = Probably favours the comparison
1 = Probably favours the intervention
10 = Favour the intervention
Conclusions

Summary of judgements

Type of recommendation

Recommendation

The panel suggests adding bedaquiline to a WHO recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low certainty of the evidence):

- An effective treatment regimen containing four recommended second line drugs in addition to pyrazinamide, according to WHO recommendations cannot be designed.
- There is documented evidence of resistance to any fluoroquinolone in addition to MDR.

In addition:

- A duly informed decision making-process by patients should be followed.
- Bedaquiline should be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol use, due to limited or no information.
- Bedaquiline should be used for a maximum duration of six months with suggested doses (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks).
- Bedaquiline must not be added alone to a failing regimen.
- Baseline testing and monitoring for QT prolongation and development of arrhythmia is imperative.
- Clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place.
- In the absence of a specific bedaquiline DST assay, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs).
**Implementation considerations**

- **Overall**
  - Extensively drug-resistant

  - A process to ensure informed decision making by patients should be established.
  - Equipment for baseline testing and monitoring for QT prolongation and development of arrhythmia should be available.
  - Monitoring of cardiac and liver disease should be available.

**Monitoring and evaluation**

- **Overall**
  - Extensively drug-resistant

  - Spontaneous reporting of adverse drug reactions should be reinforced at country level and active pharmacovigilance should be established among patient groups treated with the drug.
  - Resistance to bedaquiline should be monitored.
  - Resistance to other anti-TB drugs should be monitored following WHO recommendations.
A process to ensure informed decision making by patients should be established.
Equipment for baseline testing and monitoring for QT prolongation and development of arrhythmia should be available.
Monitoring of cardiac and liver disease should be available.

Spontaneous reporting of adverse drug reactions should be reinforced at country level and active pharmacovigilance should be established among patient groups treated with the drug.
Resistance to bedaquiline should be monitored.
Resistance to other anti-TB drugs should be monitored following WHO recommendations.
Evidence-to-recommendations template, adapted from Health system and public health evidence to recommendations framework (Version 2)\(^1\)

**PICO Question:**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Judgements</th>
<th>Research evidence</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are a large number of people affected?</td>
<td>Yes No Probably No Uncertain Probably Yes Yes Varies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
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<tr>
<td>Are the desirable anticipated effects large?</td>
<td>Yes No Probably No Uncertain Probably Yes Yes Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits &amp; harms of the options</td>
<td>Yes No Probably No Uncertain Probably Yes Yes Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the undesirable anticipated effects small?</td>
<td>Yes No Probably No Uncertain Probably Yes Yes Varies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The official tool of GRADE and DECIDE

http://www.guidelinevelopment.org/
> 80 organizations have adopted it

- Cochrane Collaboration
- WHO
- NICE
- SIGN
- Spanish CPGs Program
- Electronic resources
- ECIBC will be using it
Thank you!

GRADE
http://www.gradeworkinggroup.org

iEtD
ietd.epistemonikos.org

Guideline development tool (GDT)
http://www.guidelinedevelopment.org

DECIDE
http://www.decide-collaboration.eu/

The DECIDE project has received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013) under Grant Agreement no 258583