Holger Schünemann, MD, PhD
Professor and Chair, Dept. of Clinical Epidemiology & Biostatistics
Professor of Medicine
Michael Gent Chair in Healthcare Research
McMaster University, Hamilton, Canada
@schunemann_mac

DECIDE project conference, June 2 2014

GRADE: What Does It Offer To Guideline Producers?

Disclosure

- Co-chair GRADE Working Group
- World Health Organization: various committees
  - Co-director, WHO collaborating center on evidence informed policy making
- Cochrane Collaboration – Steering group
- GIN – Board of Directors
- No direct financial COI

GRADE

Key messages

- Methods application and research
  - Guideline development
  - DECIDE project
- Network
- Support to decision makers
  - Direct
  - Indirect

GRADE working group

- International contributors (>300) with diversity in background beginning in 2000
- Developed a unifying, transparent and sensible system for grading the quality of evidence and developing recommendations
- First articles in 2003 & 2004
- 2008 BMJ series > 1250 citations
- 2011 JCE series
- Various other publications (incl. GRADE Handbook)
- Over 70 organizations adopted or use GRADE

WHO

SIGN Scottish Intercollegiate Guidelines Network

NHS National Institute for Health and Clinical Excellence

THE COCHRANE COLLABORATION®

ACP American College of Physicians

Canadian Task Force on Preventive Health Care
Putting Prevention Into Practice

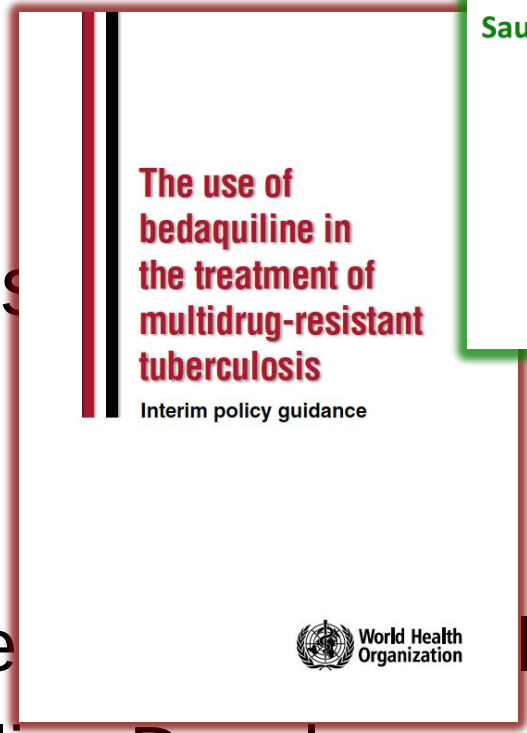
Canadian Agency for Drugs and Technologies in Health

CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, RCCM 2006, Chest 2006, BMJ 2008, JCE 2011-2012


GRADE

Rest of today's presentation

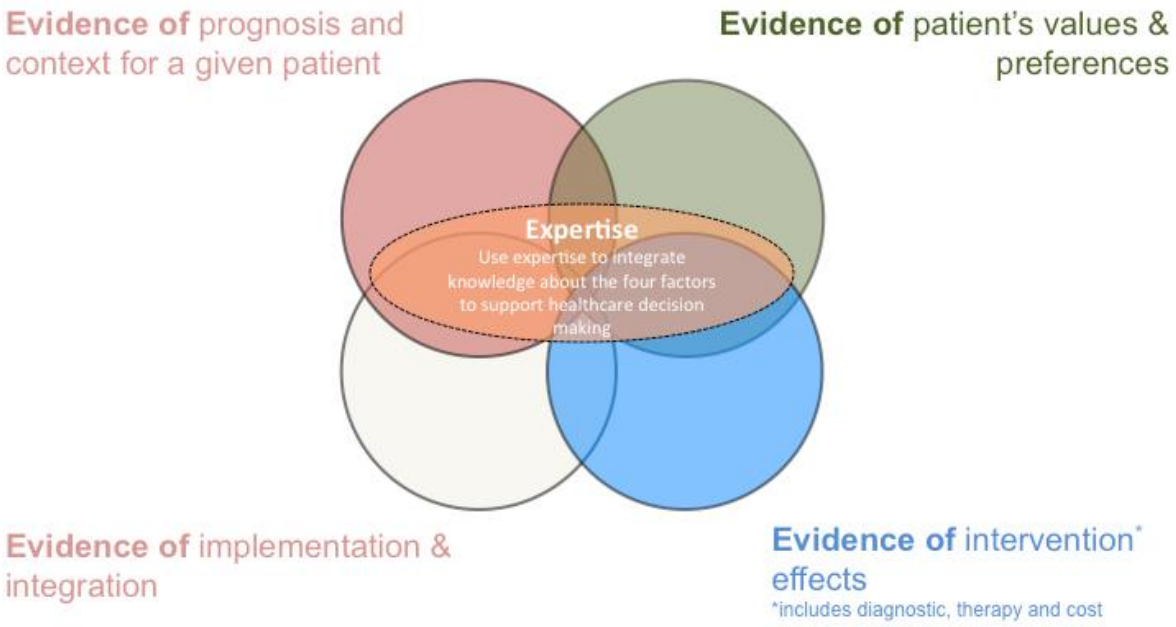
- Process of using GRADE
- Structure
  - Examples
- Criteria for decis
- Guidance
- Tools
  - Guideline Deve list (GDC)
  - GRADE Guideline Development Tool (G_2DT)



Guidelines…

… are recommendations intended to **assist** providers and recipients of health care and other stakeholders to make **informed decisions**.

WHO 2003, 2007



Schünemann and Guyatt, 2013

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process

Formulate question

Select outcomes

Rate importance

Outcomes across studies

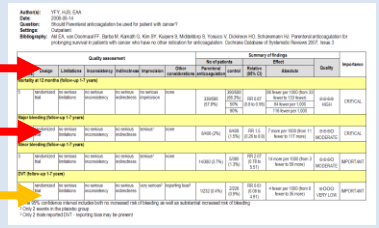
Create evidence profile with GDT

Rate quality of evidence for each outcome

Randomization raises initial quality
RCTs: high
Observational: low

P
I
C
O

Outcome — Critical
Outcome — Critical
Outcome — Important
Outcome — Not important



High
Moderate
Low
Very low

Summary of findings & estimate of effect for each outcome

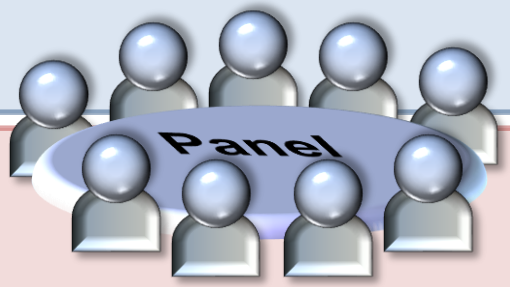
Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Opposing bias & Confounders

Evidence synthesis (SR, HTA)



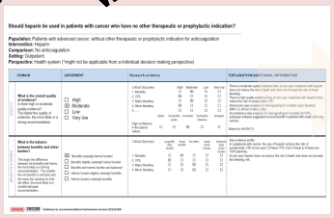
Recommendation/Decision

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

Grade recommendations (Evidence to Decision)
- For or against (direction) ↓↑
- Strong or conditional/weak (strength)

By considering balance of consequences (evidence to recommendations):
- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences
- ❑ Feasibility, equity and acceptability
- ❑ Resource use (if applicable)

EtD framework with GDT



Guideline/Decision

Formulate Recommendations/Decision
"The panel recommends that ….should..."
"The panel suggests that ….should..."
"The panel suggests to **not** ..."
"The panel recommends to **not**..."

Transparency, clear, actionable
Research?

CMAJ RESEARCH

Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise

Holger J. Schünemann MD PhD, Wojtek Wiercioch BHSc, Itziar Etxeandia Pharm D, Maicon Falavigna MD PhD, Nancy Santesso MLIS, Reem Mustafa MD MPH, Matthew Ventresca BHSc, Romina Brignardello-Petersen DDM, Kaja-Triin Laisaar MD MPH, Sérgio Kowalski MD PhD, Tejan Baldeh, Yuan Zhang BHSc, Ulla Raid PhD, Ignacio Neumann MD, Susan L. Norris MD MPH, Judith Thornton PhD, Robin Harbour BSc, Shaun Treweek PhD, Gordon Guyatt MD MS, Pablo Alonso-Coello MD PhD, Marge Reinap MA, Jan Brožek MD, Andrew Oxman MD MS, Elie A. Akl MD PhD

Abstract

Background: Although several tools to evaluate the credibility of health care guidelines exist, guidance on practical steps for developing guidelines is lacking. We systematically compiled a comprehensive checklist of items linked to relevant resources and tools that guideline developers could consider, without the expectation that every guideline would address each item.

Methods: We searched data sources, including manuals of international guideline developers, literature on guidelines for guidelines (with a focus on methodology reports from international and national agencies, and professional societies) and recent articles providing systematic guidance. We reviewed these sources in duplicate, extracted items for the checklist using a sensitive approach and developed overarching topics relevant to guidelines. In an iterative omissions and involved experts in guideline development for revisions and suggestions for items to be added.

Results: We developed a checklist with 18 topics and 146 items and a webpage to facilitate its use by guideline developers. The topics and included items cover all stages of the guideline enterprise, from the planning and formulation of guidelines, to their implementation and evaluation. The final checklist includes links to training materials as well as resources with suggested methodology for applying the items.

Interpretation: The checklist will serve as a resource for guideline developers. Consideration of items on the checklist will support the development, implementation and evaluation of guidelines. We will use crowdsourcing to

Competing interests: None declared. Authors of this manuscript have been involved in the development of various guideline manuals which are referenced in this article.

This article has been peer reviewed.

Correspondence to:
Holger Schünemann,
schuneh@mcmaster.ca

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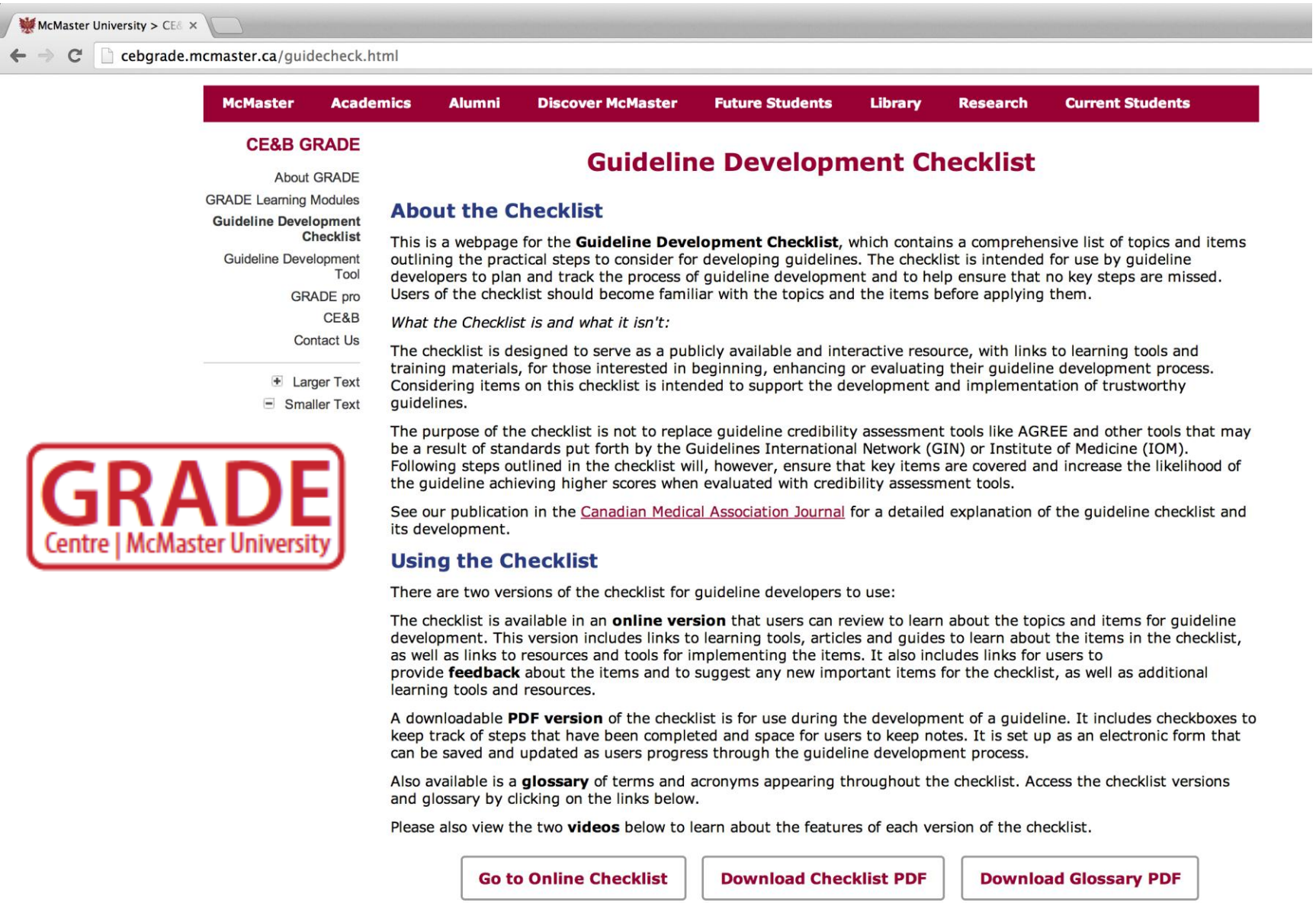
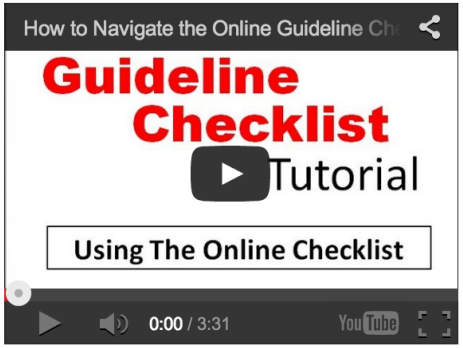
Interactive website

structure



Please also view the two **videos** below to learn about the features of each version of the checklist.

Go to Online Checklist | Download Checklist PDF | Download Glossary PDF



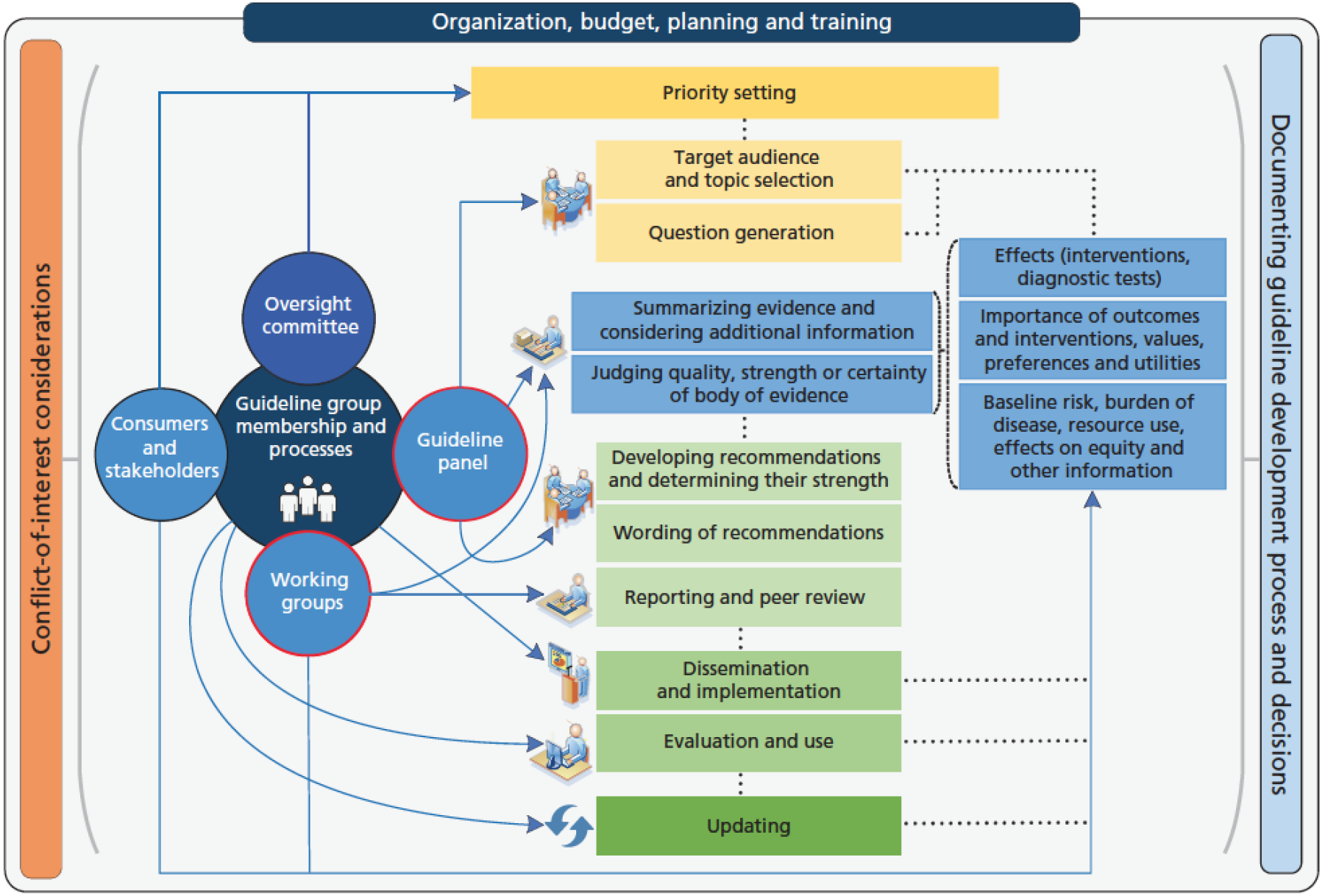
The Guideline Development Checklist is officially endorsed by:

GRADE working group

Developed in collaboration with:

AUB American University of Beirut
Estonian Health Insurance Fund
IATS
INPECS Instituto para la Excelencia Clínica y Sanitaria
McMaster University
Osteba
AWMF
RAVIJUHEND
SIGN 1993-2013
UFRGS Universidade Federal do Rio Grande do Sul
University of Aberdeen
UMKC University of Missouri-Kansas City
University of Tartu

Checklist



@schunemann_mac

GRADE applied

- Focused on management and diagnostic questions and how to use evidence to make recommendations (for health care related recommendations)

Recommendation

Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, ⊕○○○/very low quality evidence).

2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, $CHADS_2$ score = 2), we recommend oral anticoagulation rather than no therapy (Grade 1A), **aspirin (75 mg to 325 mg once daily)**

I. Prevention of allergy

1. Should exclusive breast-feeding be used in infants to prevent allergy?. *Recommendation.* We suggest exclusive breast-feeding for at least the first 3 months for all infants irrespective of their family history of atopy (conditional recommendation | low-quality evidence).

Values and preferences. This recommendation places a relatively high value on the prevention of allergy and asthma and a relatively low value on challenges or burden of breast-feeding in certain situations.

Remarks. The evidence that exclusive breast-feeding for at least the first 3 months reduces the risk of allergy or asthma is not

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PLoS MEDICINE

Health in Action

Transparent Development of the WHO Rapid Advice Guidelines

Holger J. Schünemann*, Suzanne R. Hill, Meetali Kakad, Gunn E. Vist, Richard Bellamy, Lauren Stockman, Torbjørn Fosen Wisløff, Chris Del Mar, Frederick Hayden, Timothy M. Uyeki, Jeremy Farrar, Yazdan Yazdanpanah, Howard Zucker, John Beigel, Tawee Chotpitayasunondh, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Andrew D. Oxman

D ecision criteria

Factors that can weaken the strength of a recommendation. Example: treatment of H5N1 patients with oseltamivir	Decision	Explanation
Lower quality evidence	☒ Yes ☐ No	The quality of evidence is very low.
Uncertainty about the balance of benefits versus harms and burdens	☒ Yes ☐ No	The benefits are uncertain because several important or critical outcomes were not measured.
Uncertainty or differences in values	☒ Yes ☐ No	All patients and care providers would accept treatment for H5N1 disease.
Marginal net benefits or downsides	☐ Yes ☒ No	The potential benefit is very large despite potentially small relative risk reductions.
Uncertainty about whether the net benefits are worth the costs	☐ Yes ☒ No	For treatment of sporadic patients the price is not too high.

Frequent "yes" answers will increase the likelihood of a weak recommendation.

doi:10.1371/journal.pmed.0040119.g003

LL videnceto decision tables

Schünemann et al. PLOS Med & Lancet ID, 2007

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: going from evidence to recommendations

Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Evidence to decision

- Question/Problem
- Benefits and harms
  - Quality of evidence
  - Values
- Resources
- Equity
- Acceptability
- Feasibility
- Recommendation
- Implementation

Should ACP recommend dietary interventions for preventing kidney stones recurrence?

Population: Adults with a history of one or more past kidney stones episodes ***Intervention:*** dietary interventions (individual or multicomponent, including empiric dietary interventions or diets tailored to patie characteristics) ***Comparison:*** placebo, usual care, no treatment or any other active treatment ***Setting:*** outpatients ***Perspective:*** individual patient	***Background:*** Lifetime incidence of kidney stones is 13% for men and 7% for women. After a symptomatic stone event, the 5-year recurrence rate is 35% to 50% without specific treatment. Annual direct costs in the United States may exceed $4.5 billion. Optimum management to prevent recurrent kidney stones is uncertain.

	DOMAIN	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS/EXPLANATIONS
PROBLEM	**Is the problem a priority?**	☐ No ☐ Probably No ☐ Uncertain Probably Yes ☐ Yes ☐ Varies	The lifetime incidence of kidney stones is approximately 13% for men and 7% for women. Although kidney stones may be asymptomatic, potential consequences include abdominal and flank pain, nausea and vomiting, urinary tract obstruction, infection, and procedure-related morbidity. The 5-year recurrence rate in the absence of specific treatment is 35 to 50 percent. Direct medical expenditures associated with kidney stones may exceed $4.5 billion annually in the United States.	Reports conflict regarding whether or not incidence is rising overall, but consistently indicate rising incidence in women and a falling male-to-female ratio. Risk of kidney stones may increase due to medical conditions such as primary hyperparathyroidism, obesity, diabetes, gout, and intestinal malabsorption, and due to anatomic abnormalities such as medullary sponge kidney and horseshoe kidney.
BENEFITS & HARMS	**Is there certainty in the relative importance or values of the main outcomes of interest?**	☐ Agree ☑ Somewhat agree ☐ Uncertain ☐ Somewhat disagree ☐ Disagree	Τηε ρελατιϖε ιμπορτανχε ορ ϖαλυεσ οφ τηε μαιν ουτχομεσ οφ ιντερεστ: Outcome / Relative importance / Certainty of the evidence Symptomatic recurrence — Critical Composite recurrence — Critical Radiographic recurrence — Important Withdrawals — Important Certainty of the evidence (all outcomes): No research evidence was identified but assumptions seem clear	Values and preferences are considered from patients perspective. No formal assessment of patient's values and preferences, and no evidence found. However, considering the outcomes listed, their relative importance appears clear.
	What is the balance of the benefits and harms/burden?	☑ Benefits outweigh harms/burden* ☐ Benefits slightly outweigh harms/burden ☐ Benefits and harms/burden are balanced ☐ Harms/ burden slightly outweigh benefits ☐ Harms/ burden outweigh benefits	*Critical and important Outcomes:* (Large benefit / Small benefit / No effect / Small harm/burden / Modest harm/burden) 1. Symptomatic recurrence[a]: ☐ ☑ ☐ ☐ ☐ 2. Composite recurrence: effective interventions[b]: ☑ ☐ ☐ ☐ ☐ 2. Composite recurrence: non effective interventions[c]: ☐ ☐ ☑ ☐ ☐ 4. Radiographic recurrence[d]: ☐ ☐ ☑ ☐ ☐ 4. Withdrawals[e]: ☐ ☐ ☑ ☐ ☐	* For interventions that showed statistically significant effects. For other interventions, the balance is less clear. [a] Reduced soft-drink intake vs. no treatment showed a RR 0.83 (95% CI 0.71; 0.98) [b] Effective interventions were: increased fluid intake vs. control (RR 0.45, 95% CI 0.24; 0.84), low protein and sodium, and normal calcium vs. low calcium diet (RR 0.52, 95% CI 0.29; 0.95), tailored diet vs. uniform diet (RR 0.32, 95% CI 0.14; 0.74), and instruction on fluid and calcium intake vs. low animal protein high fiber intake [c] Non- effective interventions were decreased animal protein vs control (RR 1, 95% CI 0.52; 1.91), and increased fiber intake vs control (RR 1.18, 95% CI 0.66; 2.12) [d] No effect when comparing increased fluid intake vs control (RR 0.15, 95% CI 0.02; 1.07) [e] Low incidence (<10%) when comparinf increased fluid intake vs. no treatment. There was poor reporting for other comparisons. **Subgroups:** All trials recruited patients with calcium stones. Evidence does not support claiming subgroup effects according to baseline hypercalciuria, hyperoxaluria, or hypocitraturia. Direct evidence addressing difference of effects according to baseline urine magnesium, phosphate, potassium, pH, calcium-oxalate supersaturation, calcium-phosphate supersaturation, or uric acid supersaturation is not available.
VALUES AND PREFERENCES	**Is there similarity about how much people value the critical and important outcomes?**	☐ Similar ☑ Probably similar ☐ Uncertain ☐ Probably not similar ☐ Not similar	There is no research evidence informing about the relative importance and similarity for the main outcomes.	The guideline panel believes, based on experience with affected patients, the value of the main outcomes with respect to each other seem to be clear with little variability.
RESOURCES	**Are the resources required small?** (may skip for individual patient perspective)	☐ No ☐ Probably No ☐ Uncertain ☑ Probably Yes ☐ Yes ☐ Varies	A cost effectiveness analysis showed that the cost of the treatment of recurrent kidney stones using dietary interventions is approximately USD 234 in USA (this includes and initial medical evaluation and follow-up with urine test twice/ year)(Lotan, Urol Res 2005; 33: 223).	The cost varied across different settings. While cost in the USA where USD 234, lower cost was observed in other settings: Germany USD 32, Canada USD 54, and Turkey USD 66, UK USD 179 and Sweden (USD 196). These differences result from cost or medical evaluation and treatment using different diets. A proper systematic review of these cost is not available.
	Is the incremental cost (or resource use) small relative to the benefits?	☐ No ☐ Probably No ☐ Uncertain ☑ Probably Yes ☐ Yes ☐ Varies		The costs of ureterescopy and stone fragmentation is USD 4185 in the USA (Lotan, Urol Res 2005; 33: 223). Thus, the cost of prevention appears much lower than that of treatment due to recurrence. Since the effective dietary interventions seem to have a large effect, the costs would
EQUITY	**What happens to health inequities?**	☐ Increased ☐ Probably increased Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies	No evidence was identified addressing this domain.	It is likely that this intervention has no impact on inequities but there is uncertainty.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	☐ No ☐ Probably No ☐ Uncertain Probably Yes ☐ Yes ☐ Varies	Dietary interventions are non-invasive and easy to administer. Some of the treatments that seem to be effective could potentially have a high compliance than others; however, all of them have high acceptability. Sustainability of the intervention (i.e. adherence) is uncertain.	
FEASIBILITY	**Is the option feasible to implement?***	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes Yes ☐ Varies	No evidence was identified addressing this domain.	Some of the effective options are more feasible to implement than the others (for example, increase fluid intake seems to be more feasible to implement than tailored diet); however, all of them are feasible.

Recommendation

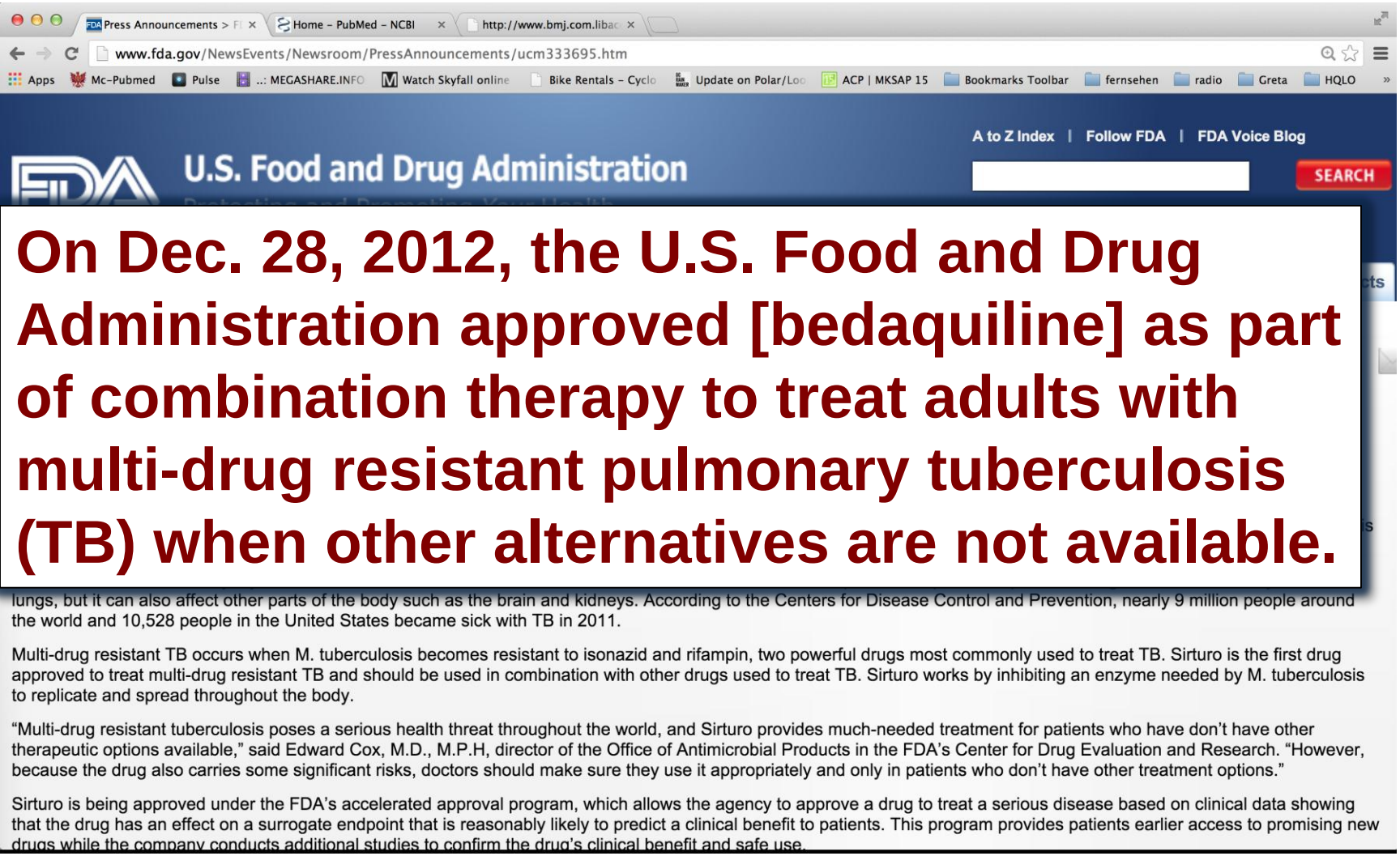
Should ACP recommend any dietary intervention for preventing kidney stones recurrence?

Overall balance of consequences	*Undesirable consequences clearly outweigh desirable consequences*	*Undesirable consequences probably outweigh desirable consequences*	The balance between desirable and undesirable consequences is too uncertain*	The balance of desirable and undesirable consequences indicates they are very similar*	*Desirable consequences probably outweigh undesirable consequences*	*Desirable consequences clearly outweigh undesirable consequences*
	☐	☐	☐	☐	☑	☐
	We recommend against the option or for the alternative	*We suggest not to use the option or to use the alternative*	*No recommendation*		*We suggest using the option*	*We recommend the option*
	☐	☐			☑	☐

Panel decisions *Describe decision making process if relevant*

Recommendation (text) ACP suggests using the following dietary interventions in patients at risk of recurrent kidney stones:

Examples



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U.S. Food and Drug Administration

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SEARCH

On Dec. 28, 2012, the U.S. Food and Drug Administration approved [bedaquiline] as part of combination therapy to treat adults with multi-drug resistant pulmonary tuberculosis (TB) when other alternatives are not available.

lungs, but it can also affect other parts of the body such as the brain and kidneys. According to the Centers for Disease Control and Prevention, nearly 9 million people around the world and 10,528 people in the United States became sick with TB in 2011.

Multi-drug resistant TB occurs when M. tuberculosis becomes resistant to isonazid and rifampin, two powerful drugs most commonly used to treat TB. Sirturo is the first drug approved to treat multi-drug resistant TB and should be used in combination with other drugs used to treat TB. Sirturo works by inhibiting an enzyme needed by M. tuberculosis to replicate and spread throughout the body.

"Multi-drug resistant tuberculosis poses a serious health threat throughout the world, and Sirturo provides much-needed treatment for patients who have don't have other therapeutic options available," said Edward Cox, M.D., M.P.H, director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research. "However, because the drug also carries some significant risks, doctors should make sure they use it appropriately and only in patients who don't have other treatment options."

Sirturo is being approved under the FDA's accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. This program provides patients earlier access to promising new drugs while the company conducts additional studies to confirm the drug's clinical benefit and safe use.

[bedaquline] is being approved under the FDA's accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint ...

9 patients who received [bedaquiline] died compared with 2 patients who received placebo. ….

World Health Organization

- provides TB diagnosis and treatment guidelines
- new TB pharmaceuticals developed, in particular for drug resistant TB
- demand from country programs, funders, patients, advocates, clinicians, public health officers
- new policy guideline for bedaquiline
  - independent of other decisions

Resources

- Reports
- Briefings
- Press Releases
- In Medical Journals/ Research Articles
- Multimedia
- Newsletters
- Statements, Speeches, Letters
- Op-eds & Articles
- Events & Presentations

Related articles

Press Release
First new tuberculosis drug for 50 years – works on

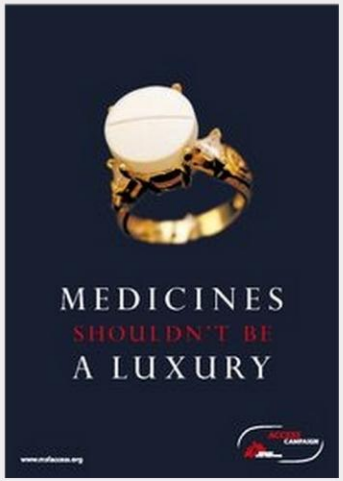
Fact Sheet: Why Bedaquiline (TMC207) should be prioritised for drug-resistant TB patients in South Africa

BACKGROUND

South Africa has one of the highest burdens of drug-resistant tuberculosis (DR-TB) worldwide, with a conservative estimate of 13,000 new cases emerging each year. [1] Treatment options for DR-TB are limited as no new drugs to treat tuberculosis (TB) have come to market in the last 50 years. To date, if treatment is failing using the few drugs available, which are mostly very expensive, have severe side effects and long treatment periods, patients are left with few other treatment options and most will die.

A new drug, bedaquiline (formerly known as TMC207) now offers hope for these patients. Yet despite positive outcomes in early clinical trials and recent agreement for a fast-track regulatory review in the United States and compassionate use in several European countries where the DR-TB burden is comparably low, the drug is not yet made available for patients in desperate need in South Africa.

Since July 2011, MSF, TAC, the Southern African HIV Clinicians Society and other concerned health activists, patients and health care workers have been pushing with the Medicines Controls Council (MCC) for bedaquiline to be made available to South African der 'compassionate use' utilising section 21 provisions of the Medicines



It is understood that there are general reservations towards compassionate use of any new drugs by some MCC advisors, with an apparent lack of safety data for bedaquiline cited by the MCC as the reason for refusing compassionate use (as only phase II has been completed).

Why does MSF believe 'compassionate use' of bedaquiline is essential?

- Lack of alternative treatment and high mortality justifies early access
- Safety data are good even though limited by small numbers of patients in trials
- Equation: potential safety risk with bedaquiline vs. certain death without is very clear. The result of delays in approval of compassionate use: patients are dying
- The WHO supports compassionate use for new drugs for DR-TB and has encouraged countries to develop specific regulatory frameworks
- Other countries with strong regulatory frameworks have approved compassionate use of bedaquiline
- There are several precedents for compassionate use in South Africa, e.g. for the malarial drug artemether and the antiretroviral lopinavir/ritonavir.

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Briefing
Fact Sheet: Why Bedaquiline (TMC207) should be prioritised for drug-resistant TB patients

First new tuberculosis drug for 50 years – works on drug-resistant forms of the disease

Médecins Sans Frontières calls for rapid registration in countries with high drug-resistant tuberculosis burden

NEW YORK/GENEVA – 31 December 2012 - Médecins Sans Frontières (MSF) welcomed the approval by the US Food and Drug Administration of bedaquiline, the first new drug active against tuberculosis (TB) to be registered since 1963.

"The first new drug to treat TB in 50 years is an immense milestone," said Dr Manica Balasegaram, Executive Director of the MSF Access Campaign. "The fact that the drug is active against drug-resistant forms of the disease makes it a potential game changer."

Today's treatment for multidrug-resistant TB (MDR-TB) is a two-year course of up to 20 different pills per day and around eight months of daily injections. Patients are subjected

Letter to FDA Opposing Approval of Bedaquiline

December 21, 2012

View as PDF.

View press release.

Public Citizen strongly opposes the accelerated approval of bedaquiline because patients taking the drug, in addition to standard TB treatment, during a phase 2 clinical trial were five times likelier to die than those who took a placebo.

January 16, 2013: FDA response to our letter

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

World Health Organization

WHO 2013

Evidence profiles

Question and source of evidence (systematic review)

Population, intervention, comparator, outcomes

Out Methods and evaluation Effect estima

Certainty/quality by outcome:

- High
- Moderate
- Low
- Very low

Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)												
2[8]	randomized trials	no serious risk of bias	no serious inconsistency	Serious[9]	very serious[5]	none	7/102[10] (6.9%)	2/105 (1.9%)	RR 3.6 (0.77 to 14.00)			
Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)												
1[11]	randomized trials	no serious risk of bias	no serious inconsistency	serious[12]	very serious[3]	none	9/79[11] (12.7%)	1/81[11] (2.5%)	RR 9.23 (1.20 to 72.95)[13,14]	10 more per 100 (from 0 more to 53 more)	+OOO Very Low	Critical
Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)												
1[15]	randomized trials	no serious risk of bias[4]	no serious inconsistency	serious[16]	serious[5]	none	n=66[1] median=83 days	n=66[1] median=125 days		median 42 days lower[17]	++OO Low	Critical

1 The mITT modified intention to treat population in C208 trial consisted of 66 subjects in each randomization group after excluding 13 subjects (16.5%) treated with bedaquiline and 15 subjects (18.5%) with placebo who did not have MDR or pre-XDR-TB at baseline or for whom MGIT results were considered not evaluable.
2 Cure defined as 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment , OR if only 1 culture is reported positive during that period, then a further 3 consecutive negative cultures from samples taken at least 30 days apart.
3 End of study data slide supplied by Janssen subsequent to US-FDA meeting. In this slide, mention is made of 'treatment success', but the company further clarified that the strict WHO definition of 'cure' was being used.
4 Representativeness of the mITT population (assumptions made for ITT population).
5 Small sample size and resulting large confidence interval limits precision: few (= serious) or very few (= very serious) observations.
6 This difference is statistically significant (Fisher p=0.005; Pearson p=0.003).

Reanalysis of trial data, contact with sponsor; overall low to very low certainty in the evidence

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Oth… cons…						
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]												
						none						
…and 2: ITT)												
					…ious[5]	none						
Mortality up to end of study at 120 weeks (C208 Sta…												

1 "phase 2" RCT evaluating cure

59 events

132 patie…

120 weeks

RR = 1.81

fo…

26/100 more patients cured

Mortality – SAE?

…events in

…) patients

…weeks

RR = 9.23 for death

10/100 more patients dead

1 The mITT modified intention to treat population i… group after excluding 13 subjects (16.5%) treated with bedaquiline and 15 subjects (18.5%) with placebo who did not have MDR or pre-XDR-TB at … uable.
2 Cure defined as 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment , OR if only 1 culture is reported positive during that period, then a further 3 consecutive negative cultures from samples taken at least 30 days apart.
3 End of study data slide supplied by Janssen subsequent to US-FDA meeting. In this slide, mention is made of 'treatment success', but the company further clarified that the strict WHO definition of 'cure' was being used.
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WHO, 2013

Table 8. The GRADE Evidence to Recommendation

In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendation safely improve patient outcomes?

Population: MDR TB patients
Intervention: bedaquiline + background MDRTB treatment
Comparison: background MDRTB treatment alone
Setting: global, MDR clinics

DOMAIN		JUDGEMENT	DETAILS OF JUDGEMENT	EVIDENCE/EXPLANATION
QUALITY	**What is the overall confidence in effect estimates?** Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation	☐ High ☐ Moderate ☐ Low ☒ Very low	*Critical Outcomes:* — *High* / *Moderate* / *Low* / *Very low* 1. Cure by 120 weeks. ☐ ☐ ☒ ☐ 2. Serious adverse events by 24 weeks ☐ ☐ ☐ ☒ 3. Mortality ☐ ☐ ☐ ☒ 4. Time to culture conversion ☐ ☐ ☒ ☐ 5. Culture conversion at 24 weeks ☐ ☐ ☒ ☐ 6. Acquired resistance to fluoroquinolones and injectable drugs ☐ ☐ ☐ ☒ *Agree* / *Somewhat agree* / *Uncertain* / *Somewhat disagree* / *Disagree* High confidence in the typical values ☐ ☒ ☐ ☐ ☐	*All critical outcomes measured* *There were concerns about imprecision (due to small sample size and few events), and indirectness (due to (1) background MDR-TB treatment not being consistent with currently recommended regimens and (2) to the use of a surrogate outcome, i.e. culture conversion). There were also concerns on the risk of bias (due to the inappropriate exclusion of 19 randomized patients with unconfirmed MDR-TB from mITT analysis).*
BENEFITS & HARMS	**What is the balance between benefits and risks/ burden?** **Are you confident that the benefits outweigh the harms and burden or vice versa?** The larger the difference between the benefits and harms, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional/weak recommendation.	☐ Benefits outweigh harms/ burden ☒ Benefits slightly outweigh harms/ burden ☐ Benefits and harms/ burden are balanced ☐ Harms/ burden slightly outweigh benefits ☐ Harms/ burden outweigh benefits	*Critical Outcomes:* — *Large/ Modest benefit* / *Small benefit* / *No effect* / *Small harm/ burden* / *Modest/ Large harm/ burden* 1. Cure by 120 weeks. ☒ ☐ ☐ ☐ ☐ 2. Serious adverse events by 24 weeks ☐ ☐ ☐ ☐ ☒ mod 3. Mortality ☐ ☐ ☐ ☐ ☒ large 4. Time to conversion ☒ large ☐ ☐ ☐ ☐ 5. Culture conversion at 24 weeks ☒ large ☐ ☐ ☐ ☐ 6. Acquired Resistance to fluoroquinolones and injectable drugs ☒ large ☐ ☐ ☐ ☐ *The issue is to balance a 23% increase in success (low confidence) vs. 5% increase in serious adverse events (very low confidence) and 10% increase in deaths (very low confidence)*	**See evidence profile** *QoE for benefits: Low due to imprecision and indirectness* *QoE for harms: Low or very low (resistance to BDQ) due to imprecision and indirectness (and risk of bias)* *No consensus was found on the balance of respective harms and benefits of addition of bedaquiline to MDRTB treatment. So a vote took place:* *- 10 experts evaluated that the benefits did outweigh the harms* *- 4 experts evaluated that the harms did outweigh the benefits* *- 2 abstained (including the chair)*

JUDGEMENT	EVIDENCE/EXPLANATION
☐ High ☐ Moderate ☐ Low ☒ Very low	*All critical outcomes measured* *There were concerns about imprecision (due*

Critical Outcomes:

	Large/ Modest benefit	*Small benefit*	*No effect*	*Small harm/ burden*	*Modest/ Large harm/ burden*
1. Cure by 120 weeks.	☒	☐	☐	☐	☐
2. Serious adverse events by 24 weeks	☐	☐	☐	☐	☒ mod
3. Mortality	☐	☐	☐	☐	☒ large
4. Time to conversion	☒ large	☐	☐	☐	☐
5. Culture conversion at 24	☒ large	☐	☐	☐	☐
		☐	☐	☐	☐

☐ Benefits outweigh harms/ burden
☒ Benefits slightly outweigh harms/ burden
☐ Benefits and harms/ burden are balanced
☐ Harms/ burden slightly outweigh benefits
☐ Harms/ burden outweigh benefits

(low confidence) vs. 5% increase
and 10% increase in deaths (very

			Agree	*Somewhat agree*	*Uncertain*	*Somewhat disagree*	*Disagree*	*Treatment success, serious adverse events and mortality were considered important to patients while time to conversion culture conversion and resistance were less so.* *The likelihood that patients would accept an effective treatment regimen would depend on subgroups of the MDR-TB population – e.g. patients with MDR-TB plus additional resistance to fluoroquinolone and/or injectable drugs may be more likely to accept the risk of taking a new drug with potential increase in mortality than patients suffering from newly diagnosed and proven MDR-TB. There is minimal variation for death, larger variation for other outcomes*
VALUES AND PREFERENCES	**What are the and preferenc** Are the assum relative values the target pop The greater th in values and the more likel recommendat	Values and preferences likely similar	☐	☐	☐	☒	☐	
RESOURCES	**Is the increm resource use) to the benefit Are the resou the expected net benefit from following the recommendation?** The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.	☐ Cost is very high relative to the net benefits						*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.)*

Recommendation						
In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendation safely improve patient outcomes?						
Overall balance of consequences	*Undesirable consequences clearly outweigh desirable consequences*	*Undesirable consequences probably outweigh desirable consequences*	The balance between desirable and undesirable consequences is too uncertain*	The balance of desirable and undesirable consequences indicates they are very similar*	*Desirable consequences probably outweigh undesirable consequences*	*Desirable consequences clearly outweigh undesirable consequences*
	☐	☐	☐	☐	☒	☐
	We recommend against the option or for the alternative	*We suggest not to use the option or to use the alternative*	*No recommendation*		*We suggest using the option*	*We recommend the option*

Panel decision: including deliberations

rms, 4 experts evaluated that the

Recommendation	*The Expert Group Panel suggests that bedaquiline may be added to a WHO recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low confidence in estimates of effect)*
Remarks and justifications	Conditions: • When an effective treatment regimen containing 4 recommended second line drugs in addition to pyrazinamide, according to WHO recommendations cannot be designed to limited or no information. • Bedaquiline should be used for a maximum duration of 6 months and at suggested dosing (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 • Spontaneous reporting of adverse drug reactions is reinforced at country level and active pharmacovigilance is established among patient groups treated with the drug;[29] • In the absence of a specific bedaquiline DST assay, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs) • Resistance to other anti-TB drugs should be monitored following WHO recommendations.

Duly informed decision-making: informed consent

Recommendation	
In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendation safely improve patient outcomes?	
Explanation	The expert group judged that the impact on culture conversion was large enough to outweigh the harms for most patients
Implementation and feasibility	• Concerns on scale-up due to costs and/or local regulatory constraints
Research gaps	• Phase 3 clinical trial(s) of safety and efficacy of bedaquiline, with particular attention to mortality (including causes of death), in the treatment of MDR-TB should be accelerated • Development of a reliable test for bedaquiline resistance • Pharmacokinetics, safety and efficacy studies in specific populations (paediatrics, HIV patients, alcohol and drug users, elderly, pregnant women, extrapulmonary TB, persons with • Acquisition of resistance to bedaquiline and to other TB drugs • Duration and dosing of treatment • Patient acceptability • Further research on the validity of culture conversion as a surrogate marker of treatment outcome
Revision planned	• By 2015 or earlier if substantial data become available increasing the knowledge on safety, toxicity and efficacy (e.g. post marketing studies, on-going trials and studies)

Implementation and feasibility

Research gaps

Phase 3 clinical trial(s) of safety and efficacy of bedaquiline ….accelerated

6. WHO Interim policy recommendations

In view of the aforementioned evidence assessment and advice provided by the EG, WHO recommends that ***bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects).***

Given the limited data available on bedaquiline and its use under the various situations that may be encountered in different clinical settings, adequate provisions for safe and effective use of the drug must be in place. Consequently, countries are advised to follow a phased approach to bedaquiline implementation, ideally through observational

5. **Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.**
    a. Special measures need to be put in place to ensure the early detection and timely reporting of adverse events using active pharmacovigilance methods, such as 'cohort event monitoring'. Any adverse drug reaction attributed to bedaquiline should also be reported to the national pharmacovigilance centre as part of the spontaneous reporting mechanism in the country. As for any other drug in the MDR-TB regimen the patient should be encouraged to report to the attending health worker any adverse event that occurs during the time the drug is being

Use of the EtD in real guidelines

+ user testing

- WHO Bedaquiline and ??? TB guideline
- World Allergy Organization guidelines on probiotics
- Rare Disease guidelines (rarebestpractices.eu)
- 10 guidelines (79 recommendations) in collaboration with the MoH in Saudi Arabia

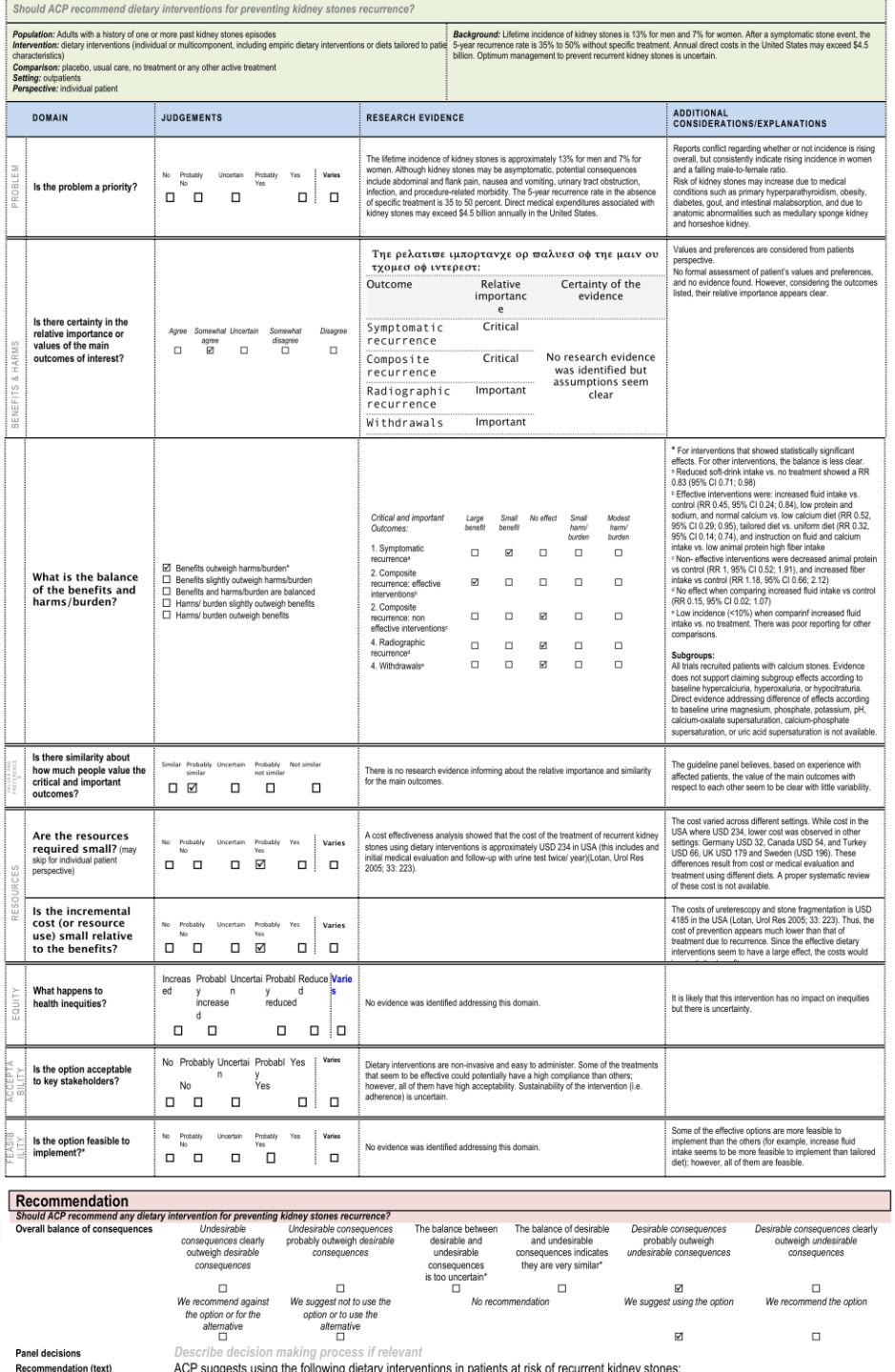
Saudi Arabian Handbook for Healthcare Guideline Development

وزارة الصحة
Ministry of Health

Adaptation Development
Adoption
Adolopment

@schunemann_mac

- Question/Problem
- Benefits and harms
  - Quality of evidence
  - Values
- Resources
- Equity
- Acceptability
- Feasibility
- Recommendation
- Implementation



Should ACP recommend dietary interventions for preventing kidney stones recurrence?

Population: Adults with a history of one or more past kidney stones episodes
Intervention: dietary interventions (individual or multicomponent, including empiric dietary interventions or diets tailored to patie characteristics)
Comparison: placebo, usual care, no treatment or any other active treatment
Setting: outpatients
Perspective: individual patient

Background: Lifetime incidence of kidney stones is 13% for men and 7% for women. After a symptomatic stone event, the 5-year recurrence rate is 35% to 50% without specific treatment. Annual direct costs in the United States may exceed $4.5 billion. Optimum management to prevent recurrent kidney stones is uncertain.

DOMAIN	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS/EXPLANATIONS
PROBLEM — **Is the problem a priority?**	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ☐ · Varies ☐	The lifetime incidence of kidney stones is approximately 13% for men and 7% for women. Although kidney stones may be asymptomatic, potential consequences include abdominal and flank pain, nausea and vomiting, urinary tract obstruction, infection, and procedure-related morbidity. The 5-year recurrence rate in the absence of specific treatment is 35 to 50 percent. Direct medical expenditures associated with kidney stones may exceed $4.5 billion annually in the United States.	Reports conflict regarding whether or not incidence is rising overall, but consistently indicate rising incidence in women and a falling male-to-female ratio. Risk of kidney stones may increase due to medical conditions such as primary hyperparathyroidism, obesity, diabetes, gout, and intestinal malabsorption, and due to anatomic abnormalities such as medullary sponge kidney and horseshoe kidney.
BENEFITS & HARMS — **Is there certainty in the relative importance or values of the main outcomes of interest?**	Agree ☐ · Somewhat agree ☑ · Uncertain ☐ · Somewhat disagree ☐ · Disagree ☐	Της ρελατισπε ιμπορτανχε ορ ϖαλυεσ οφ τηε μαιν ουτχομεσ οφ ινταερεστ: Outcome — Relative importance — Certainty of the evidence Symptomatic recurrence — Critical Composite recurrence — Critical Radiographic recurrence — Important Withdrawals — Important No research evidence was identified but assumptions seem clear	Values and preferences are considered from patients perspective. No formal assessment of patient's values and preferences, and no evidence found. However, considering the outcomes listed, their relative importance appears clear.
BENEFITS & HARMS — **What is the balance of the benefits and harms/burden?**	☑ Benefits outweigh harms/burden* ☐ Benefits slightly outweigh harms/burden ☐ Benefits and harms/burden are balanced ☐ Harms/ burden slightly outweigh benefits ☐ Harms/ burden outweigh benefits	*Critical and important Outcomes:* — Large benefit — Small benefit — No effect — Small harm/ burden — Modest harm/ burden 1. Symptomatic recurrence[a]: ☐ ☑ ☐ ☐ ☐ 2. Composite recurrence: effective interventions[b]: ☑ ☐ ☐ ☐ ☐ 2. Composite recurrence: non effective interventions[c]: ☐ ☐ ☑ ☐ ☐ 4. Radiographic recurrence[d]: ☐ ☐ ☑ ☐ ☐ 4. Withdrawals[e]: ☐ ☐ ☑ ☐ ☐	* For interventions that showed statistically significant effects. For other interventions, the balance is less clear. [a] Reduced soft-drink intake vs. no treatment showed a RR 0.83 (95% CI 0.71; 0.98) [b] Effective interventions were: increased fluid intake vs. control (RR 0.45, 95% CI 0.24; 0.84), low protein and sodium, and normal calcium vs. low calcium diet (RR 0.52, 95% CI 0.29; 0.95), tailored diet vs. uniform diet (RR 0.32, 95% CI 0.14; 0.74), and instruction on fluid and calcium intake vs. low animal protein high fiber intake [c] Non- effective interventions were decreased animal protein vs control (RR 1, 95% CI 0.52; 1.91), and increased fiber intake vs control (RR 1.18, 95% CI 0.66; 2.12) [d] No effect when comparing increased fluid intake vs control (RR 0.15, 95% CI 0.02; 1.07) [e] Low incidence (<10%) when comparinf increased fluid intake vs. no treatment. There was poor reporting for other comparisons. **Subgroups:** All trials recruited patients with calcium stones. Evidence does not support claiming subgroup effects according to baseline hypercalciuria, hyperoxaluria, or hypocitraturia. Direct evidence addressing difference of effects according to baseline urine magnesium, phosphate, potassium, pH, calcium-oxalate supersaturation, calcium-phosphate supersaturation, or uric acid supersaturation is not available.
VALUES — **Is there similarity about how much people value the critical and important outcomes?**	Similar ☐ · Probably similar ☑ · Uncertain ☐ · Probably not similar ☐ · Not similar ☐	There is no research evidence informing about the relative importance and similarity for the main outcomes.	The guideline panel believes, based on experience with affected patients, the value of the main outcomes with respect to each other seem to be clear with little variability.
RESOURCES — **Are the resources required small?** (may skip for individual patient perspective)	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☑ · Yes ☐ · Varies ☐	A cost effectiveness analysis showed that the cost of the treatment of recurrent kidney stones using dietary interventions is approximately USD 234 in USA (this includes and initial medical evaluation and follow-up with urine test twice/ year)(Lotan, Urol Res 2005; 33: 223).	The cost varied across different settings. While cost in the USA where USD 234, lower cost was observed in other settings: Germany USD 32, Canada USD 54, and Turkey USD 66, UK USD 179 and Sweden (USD 196). These differences result from cost or medical evaluation and treatment using different diets. A proper systematic review of these cost is not available.
RESOURCES — **Is the incremental cost (or resource use) small relative to the benefits?**	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☑ · Yes ☐ · Varies ☐		The costs of ureterescopy and stone fragmentation is USD 4185 in the USA (Lotan, Urol Res 2005; 33: 223). Thus, the cost of prevention appears much lower than that of treatment due to recurrence. Since the effective dietary interventions seem to have a large effect, the costs would
EQUITY — **What happens to health inequities?**	Increased ☐ · Probably increased ☐ · Uncertain ☐ · Probably reduced ☐ · Reduced ☐ · Varies ☐	No evidence was identified addressing this domain.	It is likely that this intervention has no impact on inequities but there is uncertainty.
ACCEPTABILITY — **Is the option acceptable to key stakeholders?**	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ☐ · Varies ☐	Dietary interventions are non-invasive and easy to administer. Some of the treatments that seem to be effective could potentially have a high compliance than others; however, all of them have high acceptability. Sustainability of the intervention (i.e. adherence) is uncertain.	
FEASIBILITY — **Is the option feasible to implement?***	No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ☐ · Varies ☐	No evidence was identified addressing this domain.	Some of the effective options are more feasible to implement than the others (for example, increase fluid intake seems to be more feasible to implement than tailored diet); however, all of them are feasible.

Recommendation

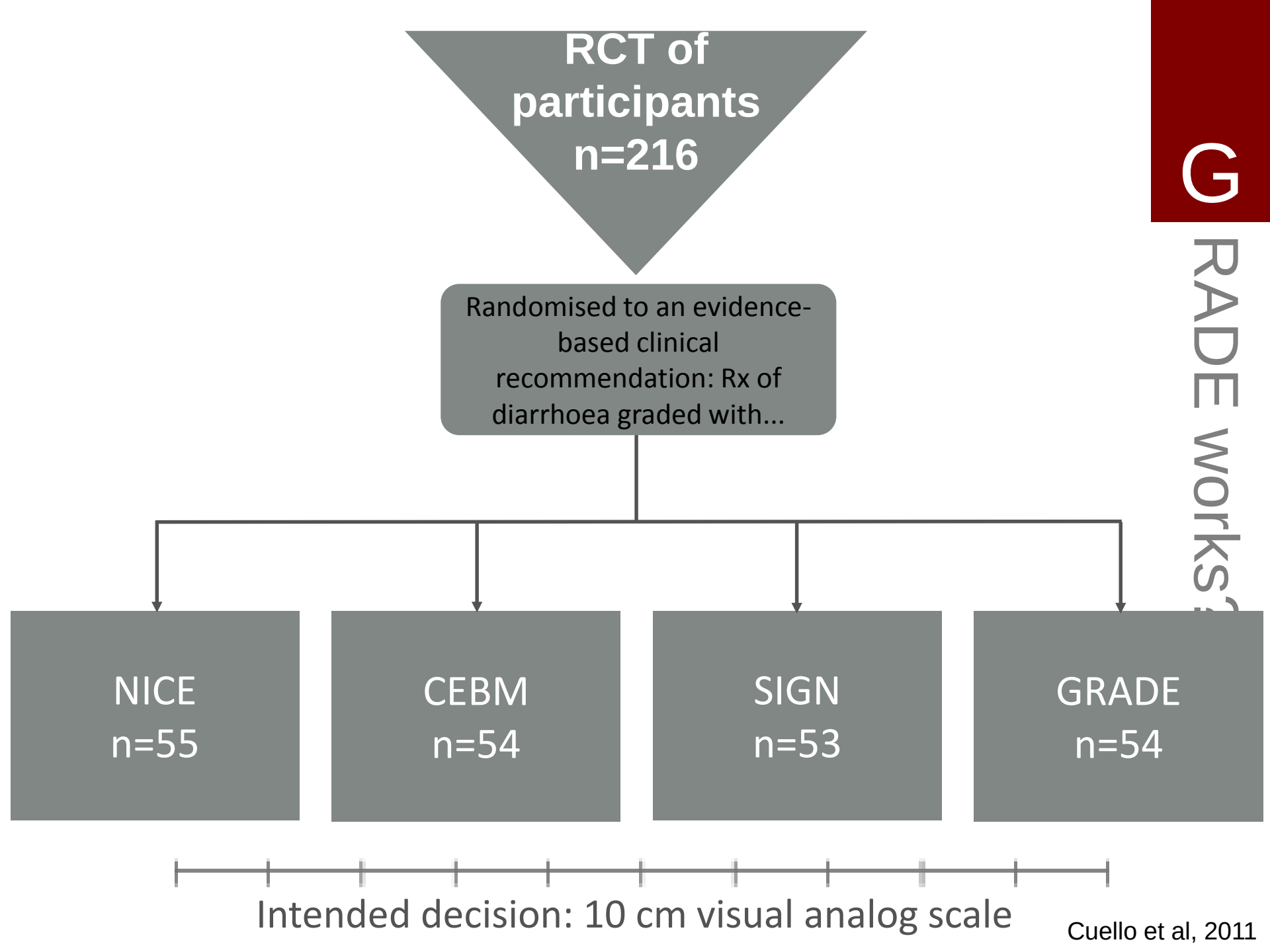
Should ACP recommend any dietary intervention for preventing kidney stones recurrence?

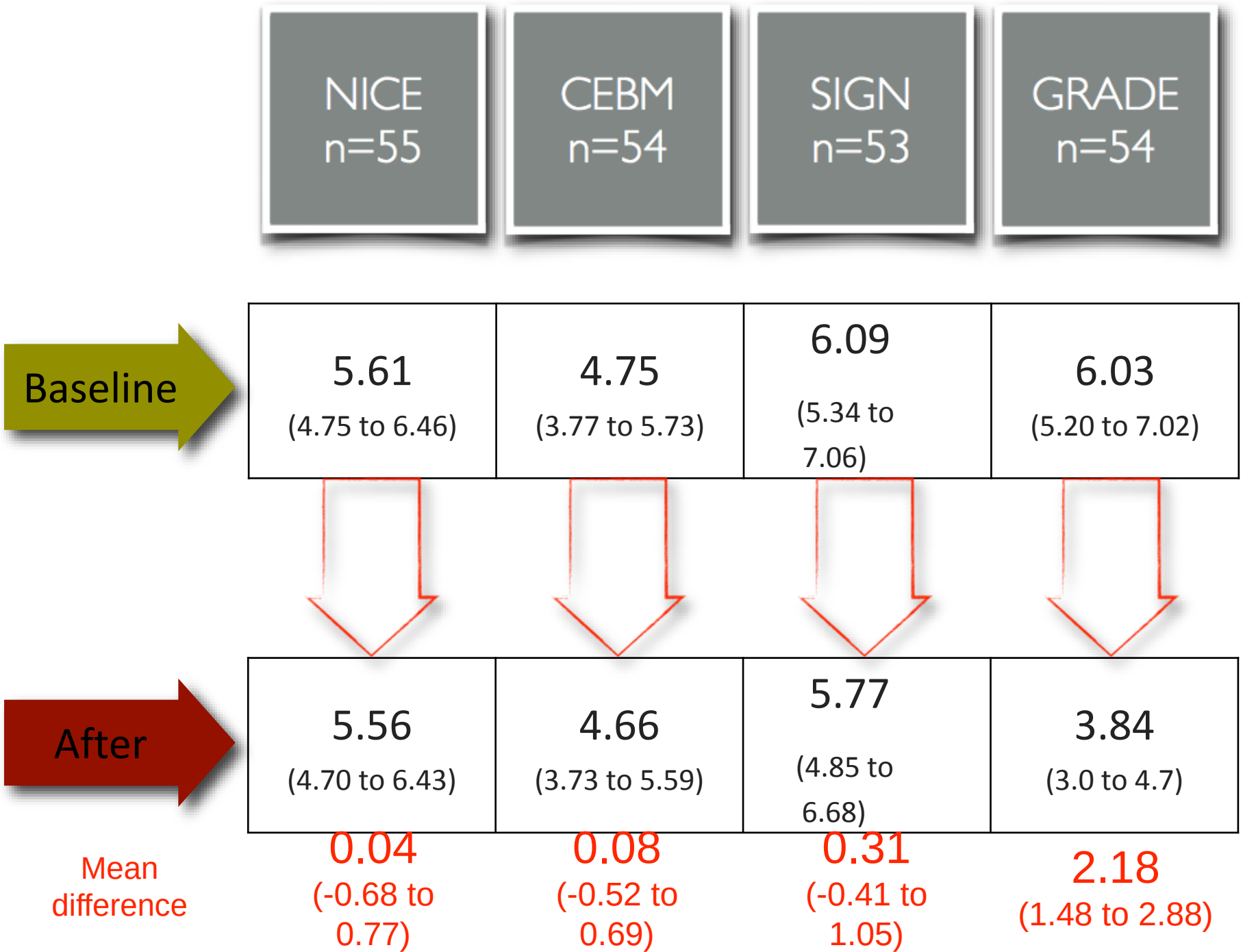
Overall balance of consequences	*Undesirable consequences clearly outweigh desirable consequences*	*Undesirable consequences probably outweigh desirable consequences*	The balance between desirable and undesirable consequences is too uncertain*	The balance of desirable and undesirable consequences indicates they are very similar*	*Desirable consequences probably outweigh undesirable consequences*	*Desirable consequences clearly outweigh undesirable consequences*
	☐	☐	☐	☐	☑	☐
	We recommend against the option or for the alternative	*We suggest not to use the option or to use the alternative*	*No recommendation*		*We suggest using the option*	*We recommend the option*
	☐	☐			☑	☐

Panel decisions — *Describe decision making process if relevant*

Recommendation (text) — ACP suggests using the following dietary interventions in patients at risk of recurrent kidney stones:

A daptment

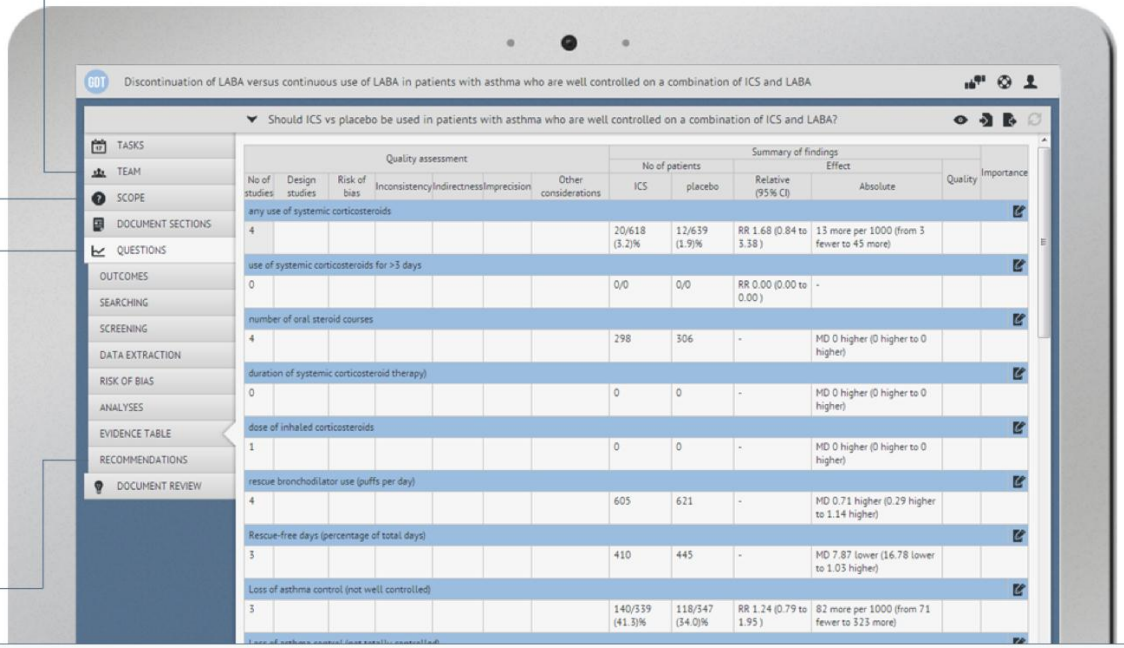

RCT of participants n=216
Randomised to an evidence-based clinical recommendation: Rx of diarrhoea graded with...
NICE n=55
CEBM n=54
SIGN n=53
GRADE n=54
Intended decision: 10 cm visual analog scale
GRADE works?
Cuello et al, 2011


NICE n=55
CEBM n=54
SIGN n=53
GRADE n=54
Baseline
5.61 (4.75 to 6.46)
4.75 (3.77 to 5.73)
6.09 (5.34 to 7.06)
6.03 (5.20 to 7.02)
After
5.56 (4.70 to 6.43)
4.66 (3.73 to 5.59)
5.77 (4.85 to 6.68)
3.84 (3.0 to 4.7)
Mean difference
0.04 (-0.68 to 0.77)
0.08 (-0.52 to 0.69)
0.31 (-0.41 to 1.05)
2.18 (1.48 to 2.88)

⊢ools

GRADE working group

- Topic proposal and selection
- Developing the scope
- Generation of structured health care questions (PICO)
- Identifying and rating importance of outcomes
- Evidence retrieval
- Designing search strategies
- Reference management
- Data extraction and management
- GRADEprofiler
- Team and stakeholder management
- Conflict of interest management
- Word processor
- Decision support tool
- Research tools



The development of GRADEprofiler (GRADEpro) has been partially supported from the European Union Seventh Framework Programme (FP7 – HEALTH.2010.3.1-1 – two stage) under grant agreement n° 258583.

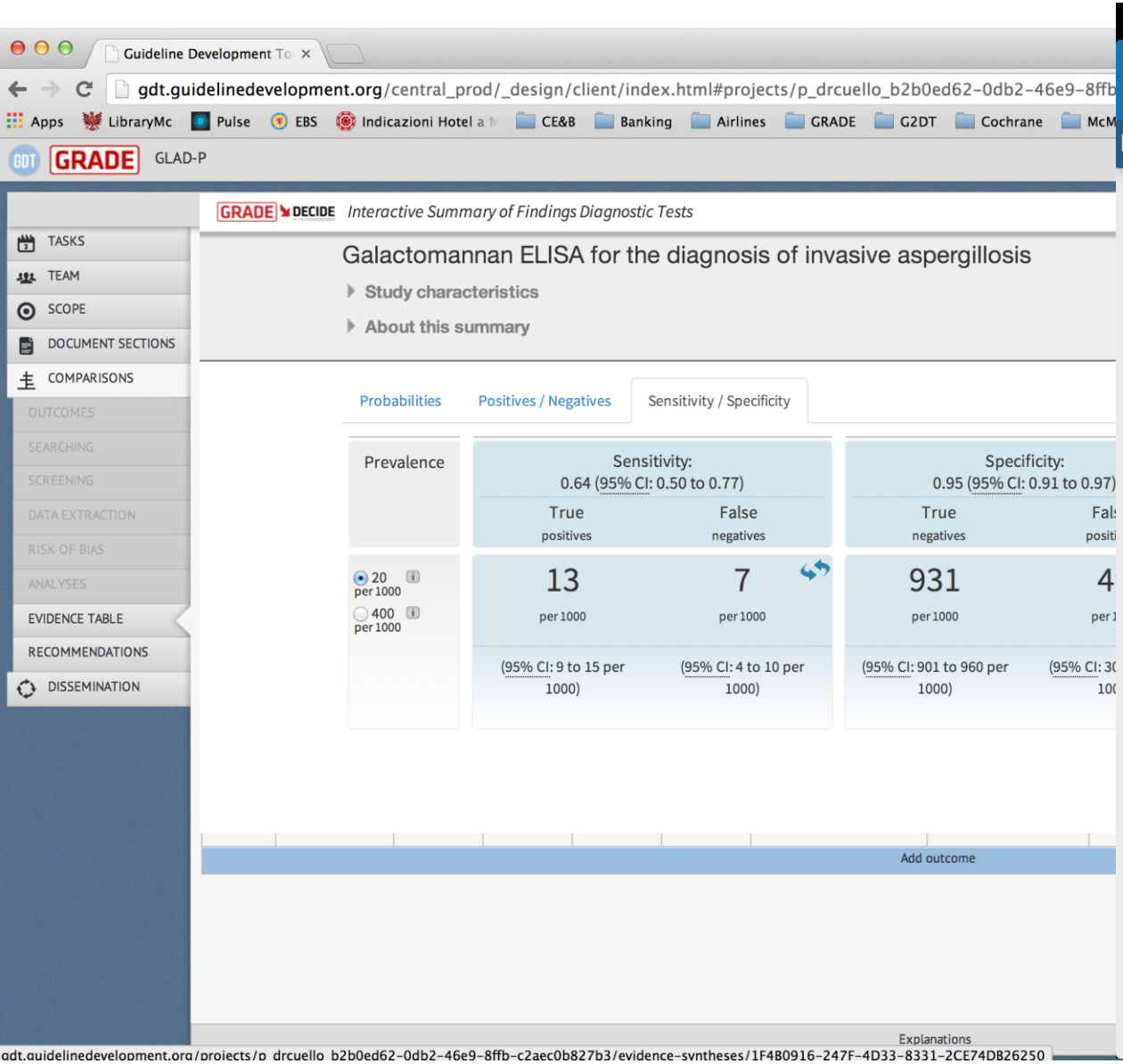
European Commission

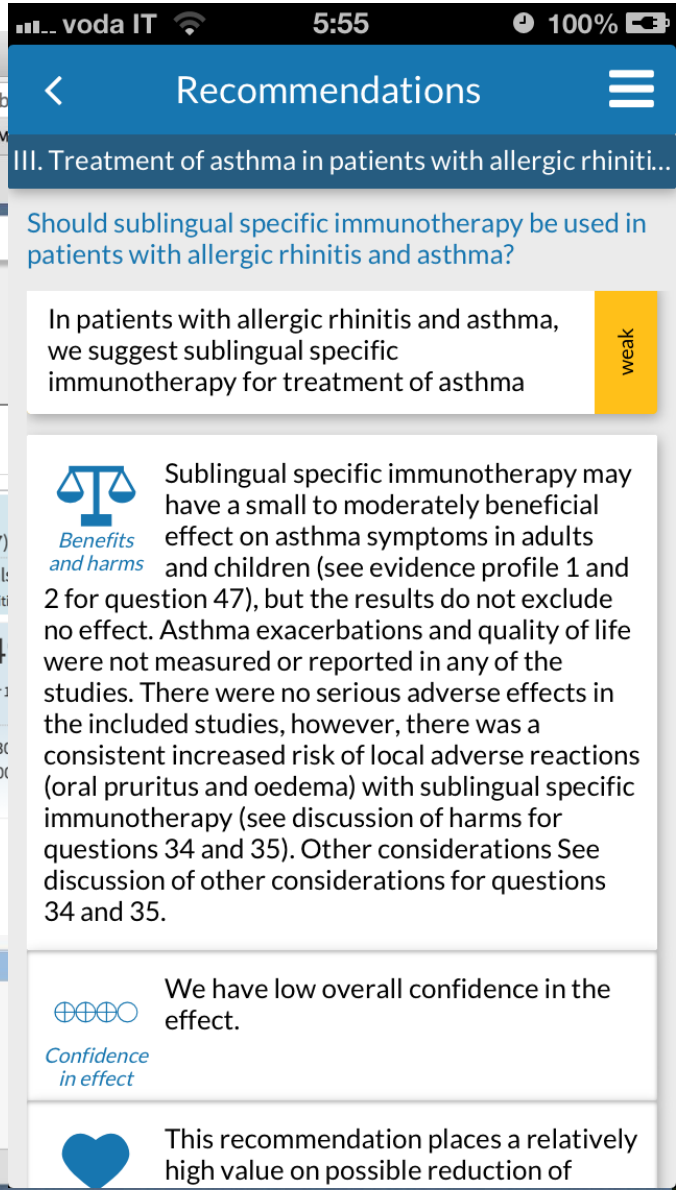
DECIDE
Developing and Evaluating GRADE Communication strategies to support Informed Decisions and practice based on Evidence

SEVENTH FRAMEWORK PROGRAMME

McMaster University
Inspiring Innovation and Discovery


G2DT





GRADE DECIDE

GRADE's ongoing work

- Evidence to decision work
- Software/electronic tool box
- Non-randomized studies – risk of bias assessment: where do we start in GRADE?
- Prognosis and risk factors
- Network meta-analysis
- Environmental health
- Rare disease

Questions

 @schunemann_mac