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21 May 2015

GRADE evidence to decision frameworks

Disclosure

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

- A few slides from Andy Oxman

This presentation

GRADE working group

- Review work on GRADE decision criteria
- GRADE Evidence to decision frameworks
  - Users
  - Use
  - Utility

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Formulate question

Select outcomes

Rate importance

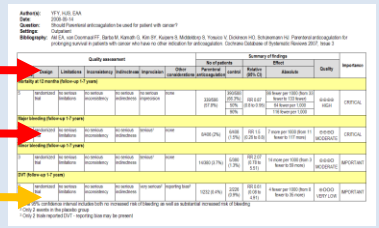
Outcomes across studies

Create evidence profile with GDT

Rate quality of evidence for each outcome

Randomization raises initial quality
RCTs: high
Observational: low

PICO		
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

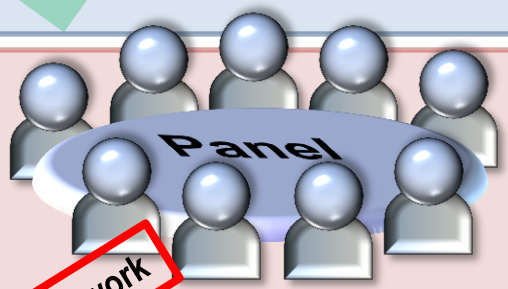
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

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

Evidence synthesis

Recommendation



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

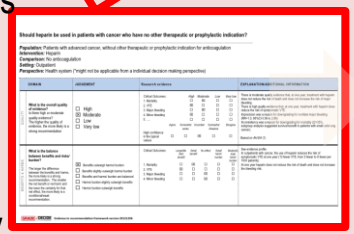
Grade recommendations (Evidence to Recommendation)

- 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



Guideline

Formulate Recommendations (↓↑ | ⊕…)

"The panel recommends that ….should..."

"The panel suggests that ….should..."

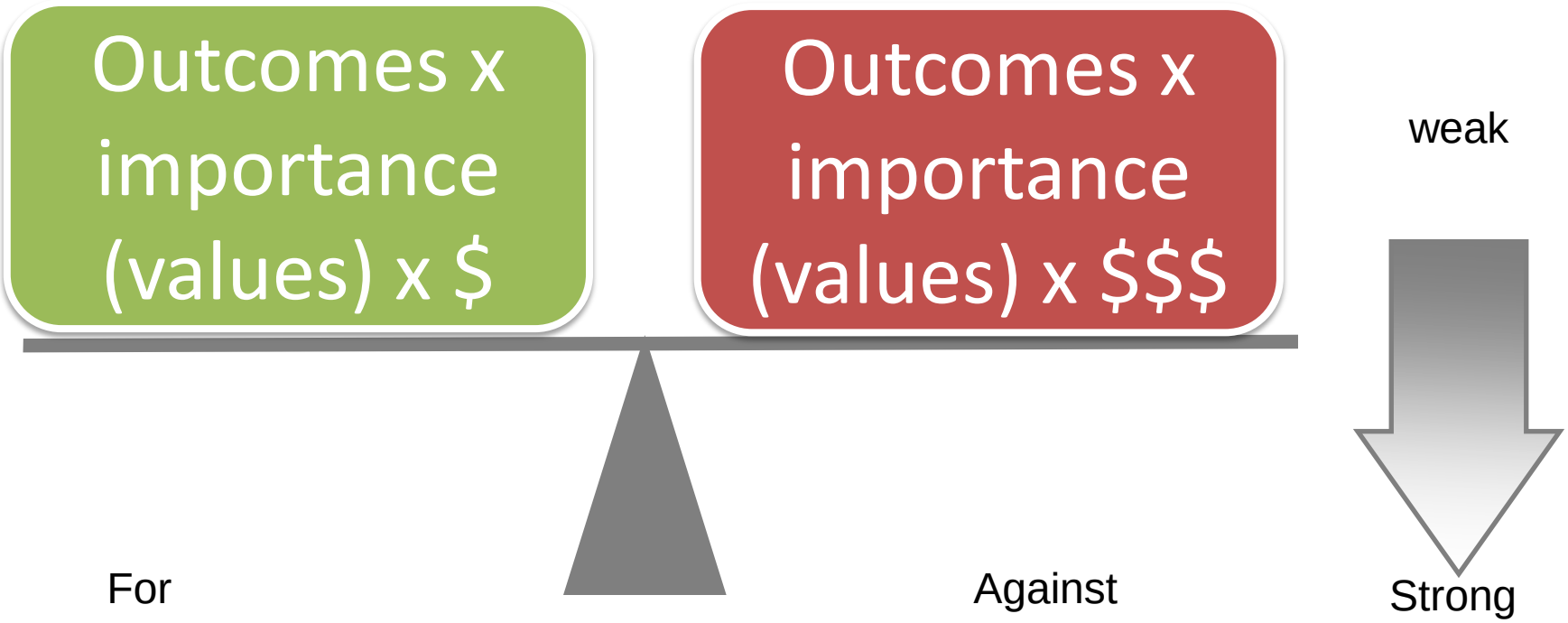
"The panel suggests to **not** ..."

"The panel recommends to **not**..."

Transparency, clear, actionable

Research?

Balancing desirable and undesirable consequences



World Health Organization guidelines

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetali Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections

Lancet Infect Dis 2007; 7: 21–31

www.figo.org

Contents lists available at SciVerse ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

SPECIAL COMMUNICATION

World Health Organization Guidelines: Use of cryotherapy for cervical intraepithelial neoplasia

Nancy Santesso [a], Holger Schünemann [a,*], Paul Blumenthal [b], Hugo De Vuyst [c], Julia Gage [d], Francisco Garcia [e], Jose Jeronimo [f], Ricky Lu [g], Silvana Luciani [h], Swee C. Quek [i], Tahany Awad [a], Nathalie Broutet [j]; for the World health Organization Steering Committee for the Recommendations on the Use of Cryotherapy for Cervical Cancer Prevention [1]

[a] McMaster University Health Sciences Centre, Hamilton, Canada
[b] Stanford University School of Medicine, Stanford, USA
[c] International Agency for Research on Cancer (IARC), Lyon, France
[d] National Cancer Institute, Washington, USA
[e] American Cancer Society, Tucson, USA
[f] PATH, Seattle, USA
[g] Jhpiego, Baltimore, USA
[h] WHO Regional Office for the Americas, Washington, USA
[i] KK Women's and Children's Hospital, Singapore
[j] World Health Organization, Geneva, Switzerland

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

Figure 3. Decisions about the Strength of a Recommendation

Schünemann et al. Lancet ID & PLOS Med 2007

LI vidence to decision tables

GRADE factors determining the direction and strength of a recommendation

Factors	Impact on the strength of a recommendation
Balance between desirable and undesirable effects	Larger the difference between the desirable and undesirable effects, more likely a strong recommendation warranted. Narrower the gradient, more likely weak recommendation warranted
Certainty (quality) of the evidence	Higher the quality of evidence, more likely a strong recommendation warranted
Relative importance of the outcomes ("values and preferences")	More variability in values and preferences, or more uncertainty in values and preferences, more likely weak recommendation warranted
Costs ("resource use")	Higher the costs of an intervention – that is, the more resources consumed – less likely a strong recommendation warranted

Recommendation: In settings where LEEP/LLETZ is available and accessible, the expert panel suggests treatment with LEEP/LLETZ over cryotherapy.

Population: Women with histologically confirmed CIN

Intervention: Cryotherapy versus LEEP

Factor	Decision	Explanation	
High or moderate evidence *(is there high or moderate quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☒ No	⊕⊕◯◯	There is moderate quality evidence from both randomised and observational controlled studies for recurrence rates. However, there is low quality evidence for other outcomes which were considered critical and important for decision making (e.g., severe adverse events, cervical cancer). There is uncertainty for fertility and other obstetrical outcomes, and HIV acquisition/transmission was not measured.
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/ weak recommendation.	☐ Yes ☒ No	Benefits of LEEP were greater, and harms were fewer or similar	▪ Recurrence rates of CIN1, CIN II-III and all CINs are probably greater with cryotherapy ○ CIN II-III, OR 3.3 (1.04 to 10.46) ○ CIN 1, OR 2.74 (0.62 to 12.07) ○ All CIN, OR 2.14 (1.05 to 4.33) ▪ Cryotherapy may be less acceptable to patients than LEEP ▪ There may be little difference in serious adverse events between cryotherapy and LEEP, but there may be fewer minor adverse events (such as pain) with cryotherapy ▪ It is unclear whether there is a difference in

EtD frameworks

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

- ***Criteria*** on which a recommendation is based
- ***Judgements*** that must be made in relation to each criterion
- ***Research evidence*** to inform each judgement
- ***Additional considerations*** that inform or explain each judgement

GRADE Evidence to Decision (EtD) framework

Can 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 (intervention)
- Considering each important factor that determine a decision (criteria)
- Providing a concise summary of the best available research evidence to inform judgements
- Helping to structure discussion and identify reasons for disagreements
- **Making the basis for decisions transparent and adaptable for target audiences**

Development of EtD frameworks

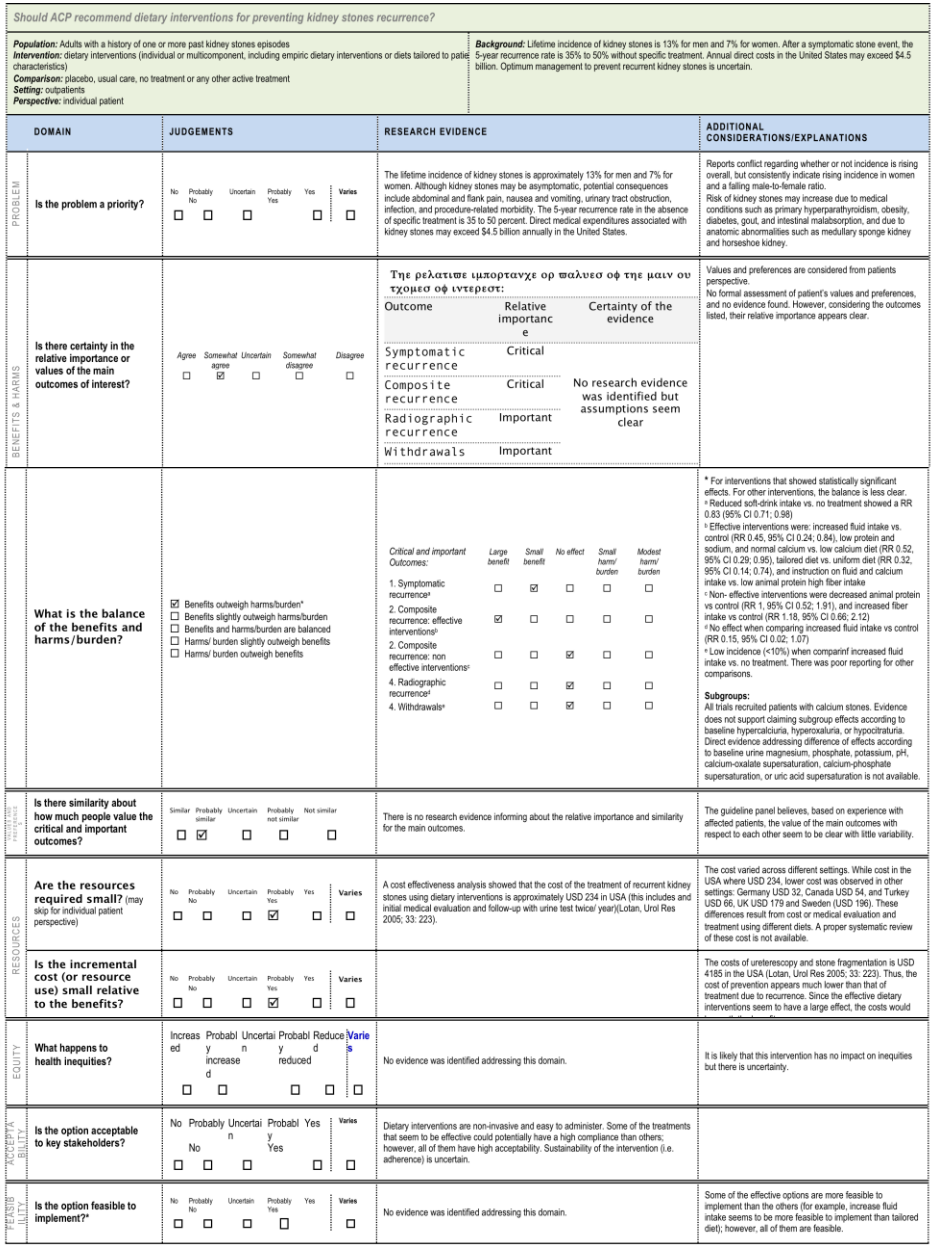
An iterative process:

- GRADE Working Group's approach
- Review of relevant literature and surveys
- Brain storming
- Feedback from stakeholders
- Application to examples
- User testing

Criteria

1. Is the problem a priority?
2. How substantial are the desirable anticipated effects?
3. How substantial are the undesirable anticipated effects?
4. What is the overall certainty of the evidence of effects?
5. Is there important uncertainty about or variability in how much people value the main outcomes?
6. Does the balance between desirable and undesirable effects favour the option or the comparison?
7. How large are the resource requirements (costs)?
8. What is the certainty of the evidence of resource requirements (costs)?
9. Does the cost-effectiveness of the intervention favour the option or the comparison?
10. What would be the impact on health equity?
11. Is the option acceptable to key stakeholders?
12. Is the option feasible to implement?

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



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 ρελατιωε ιμπορτανχε ορ ωαλυεσ οφ τηε μαιν ουτχομεσ οφ ιντερεστ: 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] Raduced 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.
UNCERTAINTY ABOUT 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 ureteroscopy 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*

GRADE DECIDE

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LU Evidence to decision

Evidence is essential to inform decisions, but requires judgments

Judgements

Desirable effects (benefits)

Are the anticipated desirable effects of the option large?

SHOW ALL | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS | [DETAILED JUDGEMENTS]

JUDGEMENTS

No	Probably no	Uncertain	Probably yes	Yes	Varies

Undesirable effects

Are the anticipated undesirable effects of the option small?

SHOW ALL | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS | [DETAILED JUDGEMENTS]

JUDGEMENTS

No	Probably no	Uncertain	Probably yes	Yes	Varies

Certainty of evidence (confidence in effect estimates)

What is the certainty of the anticipated effects?

SHOW ALL | JUDGEMENTS | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS | [DETAILED JUDGEMENTS]

JUDGEMENTS

Very low	low	Moderate	High	No direct evidence	Varies	empty

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

Interim policy guidance

World Health Organization

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

Interim policy guidance

World Health Organization

WHO 2013

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For groups making recommendations

- Question
  - Details
  - Subgroups
  - Background
- Assessment
  - Criteria
  - Judgements
  - Research evidence
  - Additional considerations
- Conclusions
  - Type of recommendation
  - Recommendation
  - Justification
  - Implementation considerations
  - Monitoring and evaluation
  - Research considerations

For groups using recommendations

- The question and background in their context
- An assessment in their context
- Decision
- Justification
- Implementation considerations
- Monitoring and evaluation

Different frameworks for different types of recommendations and decisions

- Clinical recommendations from a population perspective
- Clinical recommendations from an individual patient perspective
- Coverage decisions
- Health system and public health recommendations
- Recommendations and coverage decisions for diagnostic and other tests

Use of the EtD in real guidelines

+ user testing

- 22 guidelines (225 recommendations) in collaboration with the MoH in Saudi Arabia
- Live use of EtDs during guideline process
- Capacity building in guideline development

Guideline 'Ad-o-lopment'

Ad-o-lopment = Adaptation + Adoption + Development

1. Prioritizing questions
2. Identifying and updating existing evidence syntheses, including systematic reviews, HTAs, and evidence reports on effects of interventions
3. Systematic reviews for "other information" required for EtD
4. Developing recommendations in a structured and transparent way for a specific healthcare setting using EtDs in group meetings

Not simply adopting recommendations from previous guidelines.

The question

Key questions

1. Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?
2. Should early discharge vs. standard discharge be used for patients with acute PE?
3. Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
4. Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
5. Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
6. Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?

وزارة الصحة
Ministry of Health

The Saudi Center for
Evidence Based Health Care

Venous Thromboembolism

Clinical Practice Guideline on the Treatment of Venous Thromboembolism

April 2014

McMaster University
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Evidence profiles or Summary of Findings table

Home treatment compared to hospital treatment for patients with DVT

Patient or population: patients with patients with DVT[1,2]
Settings:
Intervention: home treatment[3,4]
Comparison: hospital treatment
Bibliography: Othieno R, Aby A, Okpo E. Home versus inpatient treatment for DVT. Cochrane database of Systematic Reviews 2007 Issue 3. Algahtani 2013

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Hospital treatment	Corresponding risk Home treatment				
Mortality	46 per 1000	33 per 1000 (21 to 53)	RR 0.72 (0.45 to 1.15)	1708 (6 studies)	⊕⊕⊖⊖ low[3,4,5,6]	
Recurrent VTE	76 per 1000	49 per 1000 (33 to 71)	RR 0.65 (0.44 to 0.94)	1769 (7 studies)	⊕⊕⊕⊖ moderate[3,4,5]	
Major bleeding	21 per 1000	14 per 1000 (7 to 29)	RR 0.67 (0.33 to 1.36)	1708 (6 studies)	⊕⊕⊖⊖ low[3,4,5,6]	
Quality of life	-	-	-	0 (3 studies[7])	⊕⊕⊖⊖ low[8,9,10]	
Post thrombotic syndrome - not reported	-	-	-	-	-	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] RCTs included recruited patients "whose home circumstances were adequate"
[2] RCTs included patients with leg DVT. They excluded those with PE and pregnant women
[3] 4 RCTs had partial hospital treatment for some participants in the home group: Levine 1996 (mean hospital stay 2.1 vs. 6.5 days in home and hospital arms respectively), Koopman 1996 (2.7 vs. 8.1 days), Boccalon 2000 (1 vs. 9.6 days), and Ramacciotti 2004 (3 vs. 7 days). Chong 2005 and Daskalopoulos 2005 did not report mean duration of hospital stay.
[4] One RCT (Baccalon 2000) used LMWH in both treatment groups. Remaining studies used LMWH in the outpatient group and UFH in the inpatient group.
[5] Of 7 RCTs, allocation was clearly concealed in 3 (unclear in 4), outcome adjudicators were clearly blinded in the 2 largest RCTs (unclear in remaining 5), missing data was significant in one small RCT, and analysis was ITT in 4 (unclear in remaining 3). These limitations did not warrant downgrading of quality of evidence, particularly because it had already been downgraded by at least one level for other reasons.
[6] CI includes values suggesting benefit and values suggesting harm
[7] Backman 2004, using EQ 5D, found no differences in mean QoL scores or in proportion of participants showing improvement in self-rated health state. Koopman 1996, using the Medical Outcome Study Short Form–20 and an adapted version of the Rotterdam Symptom Checklist, found that changes over time were similar in both arms (exception: had better scores for physical activity (P=0.002) and social functioning (P=0.001) in those receiving LMWH at the end of the initial treatment. O'Brien 1999, using SF-36 in 300 participants from Levine 1996, found no significant differ-

The GRADE EtD

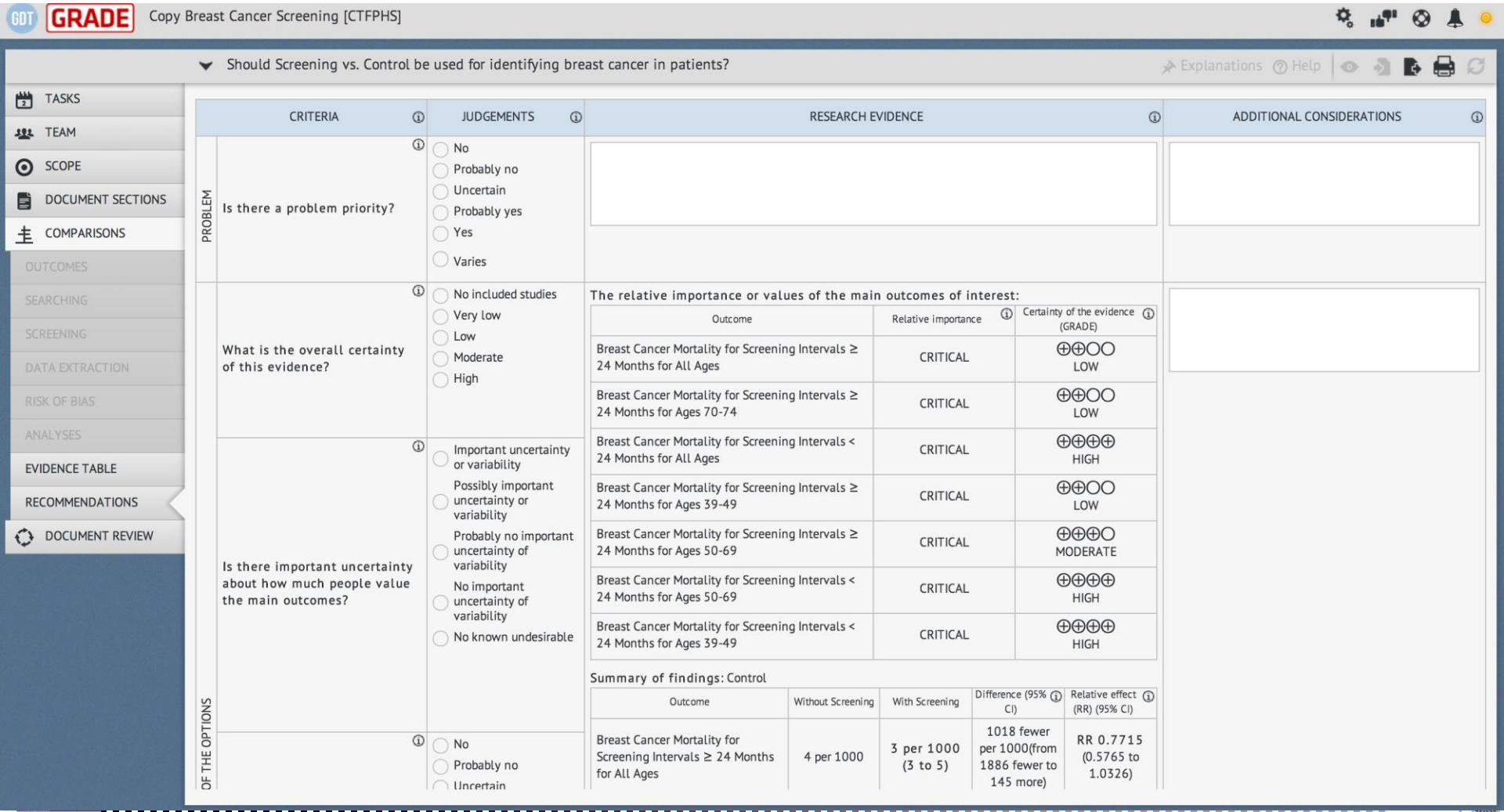
Key questions

1. Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?
2. Should early discharge vs. standard discharge be used for patients with acute PE?
3. Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
4. Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
5. Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
6. Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?

- ✓ EP or SoF Table
- ❑ Values
- ❑ Resources
- ❑ Equity
- ❑ Acceptability
- ❑ Feasibility

→ Evidence-to-Decision Framework

GRADE Evidence to Decision Frameworks (www.gradepro.org)



Appendix 1: Evidence to Decision Frameworks

Guideline Question 1: Should fibrinolysis vs. delayed percutaneous coronary intervention (PPCI) be used for treatment of STEMI in patients who present within 12 hours of symptom onset to hospitals not capable of PPCI services?

Problem: STEMI
Option: fibrinolysis
Comparison: delayed PPCI
Setting: hospitals not capable of PPCI services
Perspective: KSA MoH

Background and Objective: Timely PPCI is superior to fibrinolysis with lower rates of mortality, re-infarction and stroke. The advantage of PPCI over fibrinolysis is diminished with increasing PPCI-related time delay. This question reviews the impact of delays to treatment on outcomes of PPCI and fibrinolysis.

<table>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is there a problem priority?</td><td>○ No
○ Probably no
○ Uncertain
○ Probably yes
● Yes
○ Varies</td><td>The Saudi population has been reported to show a high burden of cardiovascular risk factors and early manifestation in a younger cohort in comparison, for example, to European populations – e.g. mean age 58 years (SD +/- 12.9) in SPACE registry study (Khan 2014, AlHabib et al 2011).

The SPACE registry study of 5055 acute coronary syndrome patients admitted to 17 hospitals in Saudi Arabia between December 2005 and December 2007 reported that 41.5% had STEMI (AlHabib et al 2011). Additionally, the GULF RACE-2 registry study conducted in 65 hospitals from 6 Arabian Gulf countries (including Saudi Arabia) between October 2008 and June 2009 reported that of 7930 patient enrolled 45.6% had STEMI, and 1-year mortality in STEMI patients was 11.5% (AlHabib et al 2012).</td><td>The panel noted that currently in the KSA, EMS services are poorly developed and that most patients transport themselves to the hospital emergency department.</td></tr>
<tr><td>Benefits & harms of the options</td><td>What is the overall certainty of this evidence?</td><td>○ No included studies
● Very low
○ Low</td><td>The relative importance or values of the main outcomes of interest:
<table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr></table></td><td>No evidence specific to KSA identified in literature search for patients' values and preferences.

Panel members, including patient representative noted that there is no</td></tr>
</table>

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		● Probably yes ○ Yes ○ Varies					
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	Re-infarction at 30 days	43 per 1000	**31 per 1000 (2 to 474)**	12 fewer per 1000 (from 41 fewer to 431 more)	**RR 0.72** (0.05 to 10.91)
			Unplanned revascularization at 30 days	43 per 1000	**63 per 1000 (6 to 649)**	19 more per 1000 (from 37 fewer to 605 more)	**RR 1.44** (0.14 to 14.92)
			Class III or IV Heart Failure at 2 weeks	375 per 1000	**240 per 1000 (135 to 431)**	135 fewer per 1000 (from 56 more to 240 fewer)	**RR 0.64** (0.36 to 1.15)
Resource use	**Are the resources required small?**	○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	No evidence identified specific to KSA and no economic evaluations identified comparing early revascularization with medical stabilization in patients with cardiogenic shock due to STEMI. Panel members considered costs and resource use when comparing early revascularization vs. medical stabilization in patients.				Panel judged resources required as probably not small considering all costs, including downstream costs (e.g. with medical stabilization, cost of extended stay in ICU and risk of heart failure in the future was considered)
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain	No evidence identified specific to KSA – Panel members considered whether the incremental costs (early revascularization vs. medical stabilization) are small relative to benefits.				Although the resources required are not small, there is a net benefit.

Recommendation
Should high volume centres vs. low volume centres be used for PPCI services?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	○	○	○	●	○

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	○	○	●	○

Recommendation	The panel suggests prioritizing the management of patients with STEMI to high volume centres. (conditional recommendation; very low quality evidence) Remark: The implementation of this recommendation should not restrict care for patients who require PPCI in settings where only low-volume centres are available.
Justification	The panel did not set any restriction on centre size, which would further reduce access. The recommendation is to prioritize expansion of existing PCI services to increase volume.
Subgroup considerations	None
Implementation considerations	Priority should be made to increase the capacity of existing low-volume centres.
Monitoring and evaluation	None
Research possibilities	Assess outcomes for patients receiving PPCI at low-volume centres vs. thrombolytics.

The Final Product

Key questions

1. Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?
2. Should early discharge vs. standard discharge be used for patients with acute PE?
3. Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
4. Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
5. Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
6. Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?

Recommendation 1:

For patients with simple acute DVT of the leg, the Saudi Expert Panel suggests home treatment over hospital treatment (conditional recommendation; moderate quality evidence)

Remarks:

- Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed
- Consider patient level of education, knowledge about the disease, and likelihood of compliance
- Consider hospital treatment for patients with severe acute DVT of the leg and patients who are apprehensive
- This recommendation applies to anticoagulation treatment with LMWH but not NOACs

Breast cancer screening

CMAJ GUIDELINES

Recommendations on screening for breast cancer in average-risk women aged 40–74 years

The Canadian Task Force on Preventive Health Care

See related commentary by Gøtzsche on page 1957 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.111721

Women aged 40–49 years

For women 40–49 years of age, we recommend not routinely screening for breast cancer with mammography. (Weak recommendation; moderate-quality evidence.)

Recommendations

Recommendation 1:

The Saudi Expert Panel suggests screening with mammography in women aged 40–49 years every 1 to 2 years. (Conditional recommendation; low-quality evidence)

Remarks:

Based on local cancer registry data, the incidence of breast cancer in the KSA seems to be higher than in the other countries in which studies were conducted. This fact may indicate that higher benefit on breast cancer mortality justifies a recommendation in favor of implementing breast cancer screening using mammography in this age group. Since the guideline panel determined that there is a close balance between desirable and undesirable consequences, they also suggest implementing shared-decision making strategies as a way to incorporate actively patients' perspective into the decision.

Reason

- Different baseline risk in Saudi Arabia

Hemodialysis

Canadian Society of Nephrology/
Société Canadienne De Néphrologie
CSN/SCN

Box 2 - Recommendation:

For adult patients (>18 years of age) with an eGFR <15 ml/min/1.73m^2, we recommend an 'intent-to-defer' over an 'intent-to-start early' approach for the initiation of chronic dialysis. (*Strong recommendation; moderate quality evidence* ⊕⊕⊕O)

Underlying Values and Preferences

This recommendation places a high value on quality of life, by avoiding the burden associated with earlier initiation of dialysis without clinical indications, while concurrently avoiding complications of uremia. This recommendation also places a high value on resource use, which increases with earlier initiation of dialysis. This recommendation places a low value on surrogate markers including serum albumin, body nitrogen and eGFR levels in the absence of symptoms...

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Message

- Complete practice change of authorities in the field
- Also true for other guidelines

Multi vessel vs single vessel intervention for myocardial infarction

National Clinical Guideline Centre

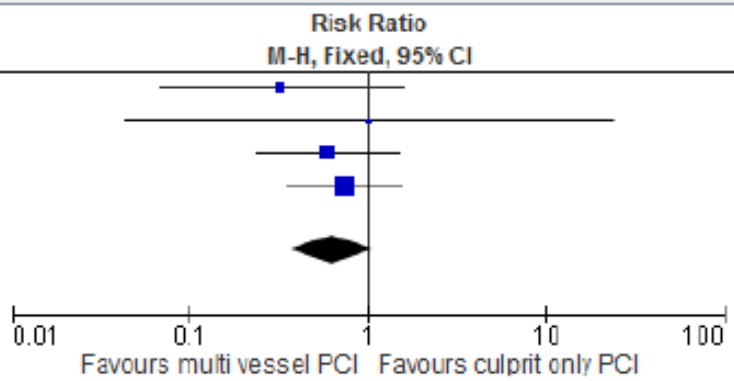
I.5 Culprit versus complete revascularisation

I.5.1 Culprit-only PPCI versus immediate multivessel PCI

Figure 180: RCTs: all-cause mortality (≤ 30 days)

Study or Subgroup	Multi vessel PCI Events	Total	Culprit only PCI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CvLPRIT 2015	2	150	6	146	17.7%	0.32 [0.07, 1.58]
Di Mario 2004	1	52	0	17	2.2%	1.02 [0.04, 23.91]
Politi 2010	6	65	13	84	33.1%	0.60 [0.24, 1.48]
Wald 2013	12	234	16	231	47.0%	0.74 [0.36, 1.53]
Total (95% CI)		**501**		**478**	**100.0%**	**0.63 [0.37, 1.05]**
Total events	21		35			

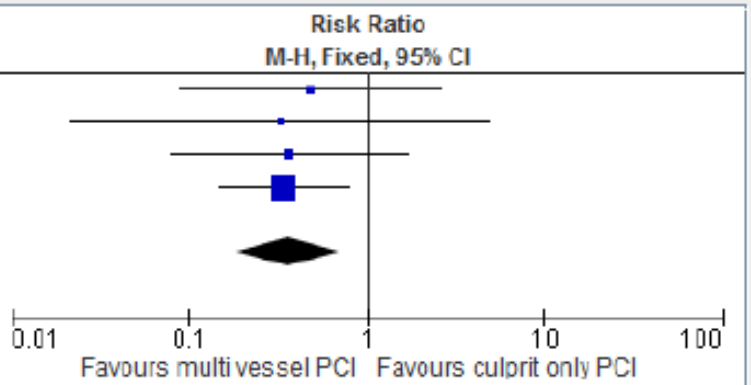
Heterogeneity: Chi² = 0.97, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)



Mortality-long term

Study or Subgroup	Multi vessel PCI Events	Total	Culprit only PCI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CvLPRIT 2015	2	150	4	146	12.7%	0.49 [0.09, 2.62]
Di Mario 2004	1	52	1	17	4.7%	0.33 [0.02, 4.95]
Politi 2010	2	65	7	84	19.2%	0.37 [0.08, 1.72]
Wald 2013	7	234	20	231	63.3%	0.35 [0.15, 0.80]
Total (95% CI)		**501**		**478**	**100.0%**	**0.37 [0.19, 0.71]**
Total events	12		32			

Heterogeneity: Chi² = 0.13, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)



Reinfarction

Two small trials vs four trials ~200 vs 1000 patients

Evidence Profile: Multi-vessel PPCI compared to culprit only PPCI in patients with STEMI and multi-vessel coronary artery disease undergoing PPCI

Author(s): Veena Manja & Wojtek Wiercioch
Date: 2014-12-15

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	multi-vessel PPCI	culprit only PPCI	Relative (95% CI)	Absolute (95% CI)		
Mortality - long term												
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	21/501 (4.2%)	35/478 (7.3%)	**RR 0.63** (0.37 to 1.05)	27 fewer per 1000 (from 4 more to 46 fewer)	⊕⊕◯◯ LOW	CRITICAL
Reinfarction												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	12/501 (2.4%)	32/478 (6.7%)	**RR 0.37** (0.19 to 0.71)	42 fewer per 1000 (from 19 fewer to 54 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Revascularization												
4	randomised trials	serious [1]	not serious	not serious	not serious	none	38/501 (7.6%)	92/478 (19.2%)	**RR 0.37** (0.26 to 0.53)	121 fewer per 1000 (from 90 fewer to 142 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Message

- Saudi Arabian panel more certain in decision/recommendation
- Reason:
  - NEW EVIDENCE IDENTIFIED during our effort

Summary

Advantages

- Builds in part on existing evidence syntheses
- Transparent consideration of factors beyond QoE (EtDs) with focus on local/regional setting
- Builds capacity

Challenges

- SRs required as starting point
- Challenging if existing SR restricted inclusion to RCTs or highly selected outcomes
- Reviews of “other information”
- Panels need to commit to follow rigorous methodological approach and stick to timelines

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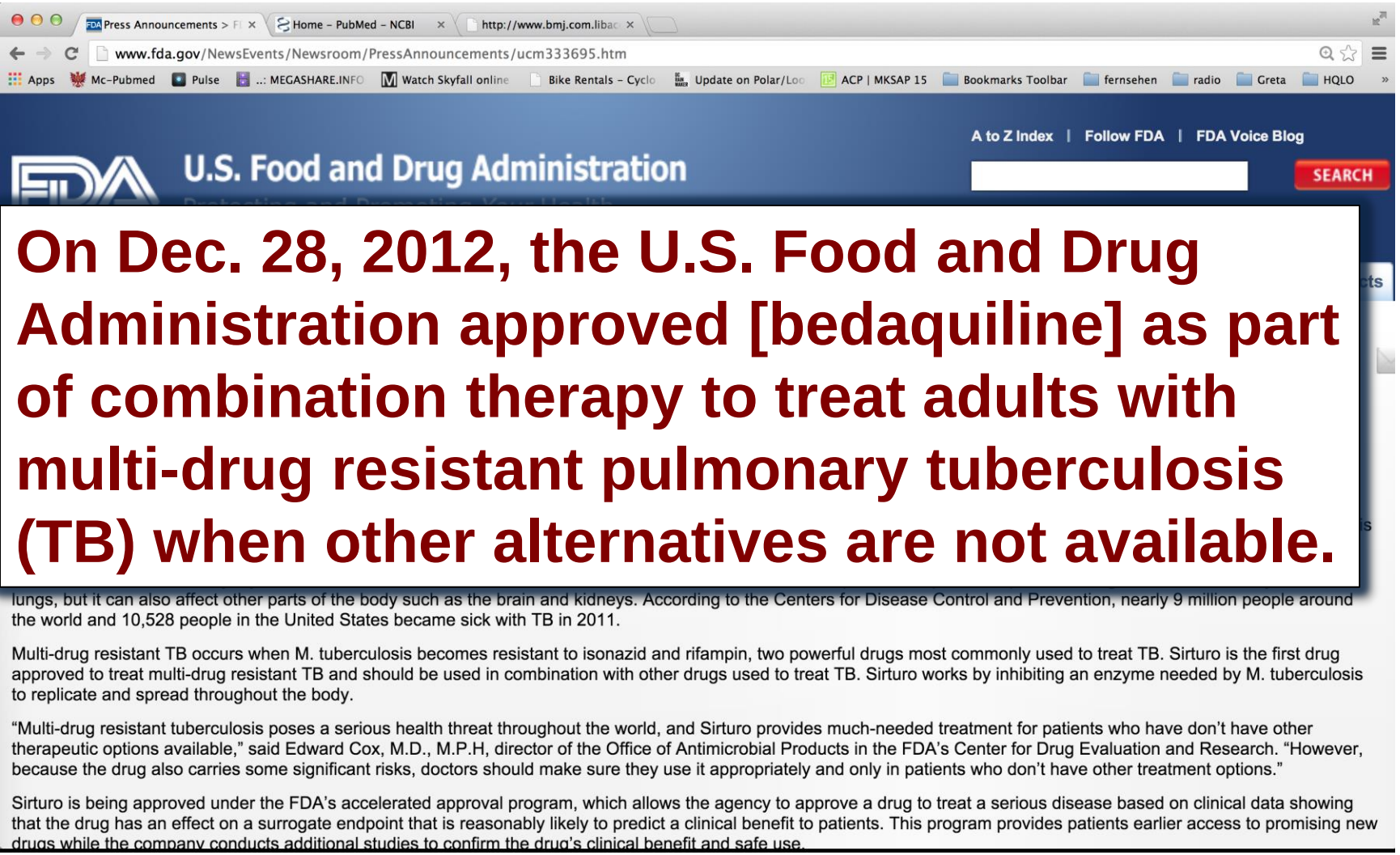
GRADE in action



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.

[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

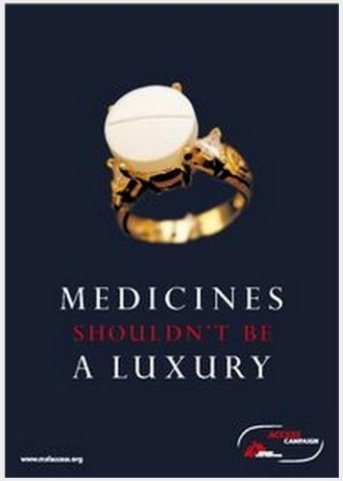
Fact Sheet: Why Bedaquiline (TMC207) should be prioritised for drug-resistant TB patients in South Africa

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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Related articles

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

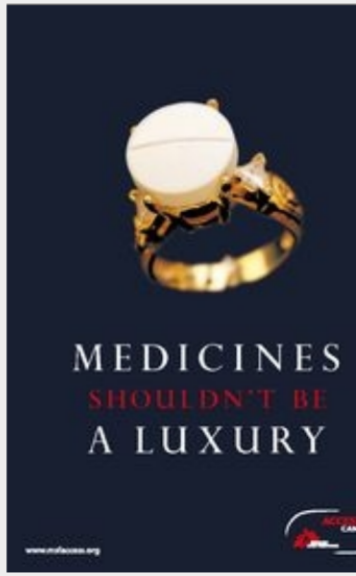
First new tuberculosis drug for 50 years – works on drug-resistant forms of the disease

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



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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

HEALTH AND SAFETY

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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	Other considerations					
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]											
1	randomized trials	no serious	no serious	no serious	no serious	none	59/79[3]	1/81[3]	RR 1.81 (1.20 to 2.73)	26 more per 100 (from 5 more to 46 more)	+OOO LOW	Critical
Mortality up to end of study at 120 weeks (C208 Stage 2: mITT and 2: ITT) [1,2]											
1	randomized trials	no serious	no serious	no serious	serious[5]	none	9/79[3]	1/81[3]	RR 9.23 (1.20 to 70.90)	10 more per 100 (from 1 more to 70 more)	+OOO LOW	Critical

1 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.

2 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.

3 Representativeness of the mITT population (assumptions made for ITT population).

4 Small sample size and resulting large confidence interval limits precision: few (= serious) or very few (= very serious) observations.

5 This difference is statistically significant (Fisher p=0.005; Pearson p=0.003).

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

WHO, 2013

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Recommendation: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment.

Other explanations

Remarks: Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time.

The panel voted on whether this recommendation should be strong or weak and there was one abstention and one dissenting vote.

Certainty in or similar values *(is there certainty or similarity?)* The more certainty or similarity in values and preferences, the more likely a strong recommendation.	☒ Yes ☐ No	Similar values across women	▪ High value was placed on CIN recurrence, serious adverse events and acceptability to the patient ▪ Low value was placed on minor adverse events
Resource implications *(are resources worth expected benefits?)* The lower the cost of an intervention compared to the alternative that is considered and other costs related to the decision – that is, fewer resources consumed – the more likely is a strong recommendation.	☒ Yes ☐ No	More resources required for LEEP	▪ Need for more skilled providers to perform LEEP ▪ Need for more or expensive equipment/supplies for LEEP; electrical supply for LEEP ▪ Need for local anaesthesia with LEEP
Overall strength of recommendation	Conditional		

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*
						☐
						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 due 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.					

Panel decision: including deliberations

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

Implications of a *strong* recommendation

- Policy makers: The recommendation can be adapted as a policy in most situations
- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not
- Clinicians: Most patients should receive the recommended course of action

Implications of a *weak/conditional* recommendation

- Policy makers: There is a need for substantial debate and involvement of stakeholders
- Patients: The majority of people in this situation would want the recommended course of action, but many would not
- Clinicians: Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making

Are the desirable anticipated effects lar	○ No ○ [illegible] no
Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies
Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ● Varies

158 more

20 more

74 fewer

Summary of findings: Control: OBR alone

Outcome	Without Delamanid plus OBR	With Delamanid plus OBR	Difference (95% CI)	Relative effect (RR) (95% CI)
Cure at 24 months	452 per 1000	610 per 1000 (466 to 737)	158 more per 1000 (from 14 more to 285 more)	RR 1.35 (1.03 to 1.63)
Serious Adverse Events	88 per 1000	108 per 1000 (53 to 204)	20 more per 1000 (from 34 fewer to 116 more)	RR 1.23 (0.61 to 2.33)
Mort[illegible]	82 per 1000	8 per 1000 (1 to 63)	74 fewer per 1000 (from 19 fewer to 81 fewer)	RR 0.1 (0.01 to 0.77)
Sputum culture conversion at two months as a surrogate for cure (assessed with MGIT liquid culture, MITT population)	296 per 1000	453 [illegible]000 628)	157 more per 1000 (from 30 more to 332 more)	RR 1.53 (1.1 to 2.12)
Sputum cul[illegible] conversio[illegible] months [illegible] for cure [illegible] solid cult[illegible] population	[illegible]	[illegible]1000 733)	202 more per 1000 (from 61 more to 397 more)	RR 1.6 (1.18 to 2.18)
Cure at 24 mon[illegible] (after treatment for ful[illegible] eight months) (assessed with: Solid culture)	771 per 1000	940 per 1000 (840 to 979)	170 more per 1000 (from 69 more to 208 more)	RR 1.22 (1.09 to 1.27)
Electrocardiogram QT prolongation	19 per 1000	51 per 1000 (11 to 152)	33 more per 1000 (from 8 fewer to 133 more)	RR 2.74 (0.6 to 8.1)
Acquired resistance to delamanid (follow-up range 24 weeks)	0 per 1000	0 per 1000 (0 to 0)	not estimable	not estimable
Time to culture conversion at two months as surrogate for cure (assessed with MGIT liquid culture, MITT population)	239 per 1000	146 per 1000 (101 to 216)	92 fewer per 1000 (from 23 fewer to 138 fewer)	HR 0.58 (0.39 to 0.89)

	There is no data on patients with diabetes and or extrapulmonary TB.
Implementation considerations	A duly informed decision making-process by patients should be followed -this includes that the intervention be presented as an option and includes information about uncertainty about the effects. In some settings, informed consent is mandatory for MDR treatment and local practice should be observed. Local practice requiring written informed consent should be observed (5:5 vote, 2 missing). With regard to QT prolongation, data were available for simultaneous use with levofloxacin, but not with moxifloxacin. No evidence is available on combined use with clofazimine. In particular, no data for the simultaneous use of bedaquiline and delamanid are available. Therefore, for this interim guidance, no recommendation about the simultaneous use of delamanid and bedaquiline or other QT prolonging drugs is being made until further data are available. This recommendation is valid for a maximum of two years and will be updated should additional data become available.

A duly informed decision making-process by patients should be followed; this includes that the intervention be presented as an option and includes information about uncertainty about the effects…Local practice requiring written informed consent should be observed (5:5 vote, 2 missing).

EtD frameworks

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

- ***Criteria*** on which a recommendation is based
- ***Judgements*** that must be made in relation to each criterion
- ***Research evidence*** to inform each judgement
- ***Additional considerations*** that inform or explain each judgement

For research translation to be evidence-based and lead to appropriate policy

messages

- structured decision-making processes
- transparent evidence syntheses that inform about the certainty in that evidence
  - evidence profiles, evidence to decision frameworks with judgments
- confidence in estimates of intervention effects only “a” part
  - bedaquiline or delamanid for TB
- accept uncertainty and be able to communicate it for better research and implementation