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

Transparent recommendations

Evidence to decision tables

- Transparent for decision making
- Not granular enough for complex decision making in health policy and public health
- Feasibility and acceptability issues important for international guideline developers
- Different decisions need adaptable frameworks
  - Coverage, health systems, diagnostic
- GRADE's DECIDE project (2011-2015)
  - Improving EtD tables

thebmj | BMJ 2016;353:i2016 | doi: 10.1136/bmj.i2016

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction

Pablo Alonso-Coello,[1,2] Holger J Schünemann,[2,3] Jenny Moberg,[4] Romina Brignardello-Petersen,[2,5] Elie A Akl,[2,6] Marina Davoli,[7] Shaun Treweek,[8] Reem A Mustafa,[2,9] Gabriel Rada,[10,11,12] Sarah Rosenbaum,[4] Angela Morelli,[4] Gordon H Guyatt,[2,3] Andrew D Oxman[4] the GRADE Working Group

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines

Pablo Alonso-Coello,[1,2] Andrew D Oxman,[3] Jenny Moberg,[3] Romina Brignardello-Petersen,[2,4] Elie A Akl,[2,5] Marina Davoli,[6] Shaun Treweek,[7] Reem A Mustafa,[2,8] Per O Vandvik,[3] Joerg Meerpohl,[9] Gordon H Guyatt,[2,10] Holger J Schünemann,[2,10] the GRADE Working Group

ELSEVIER

Journal of Clinical Epidemiology ■ (2016) ■

ORIGINAL ARTICLE

GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health

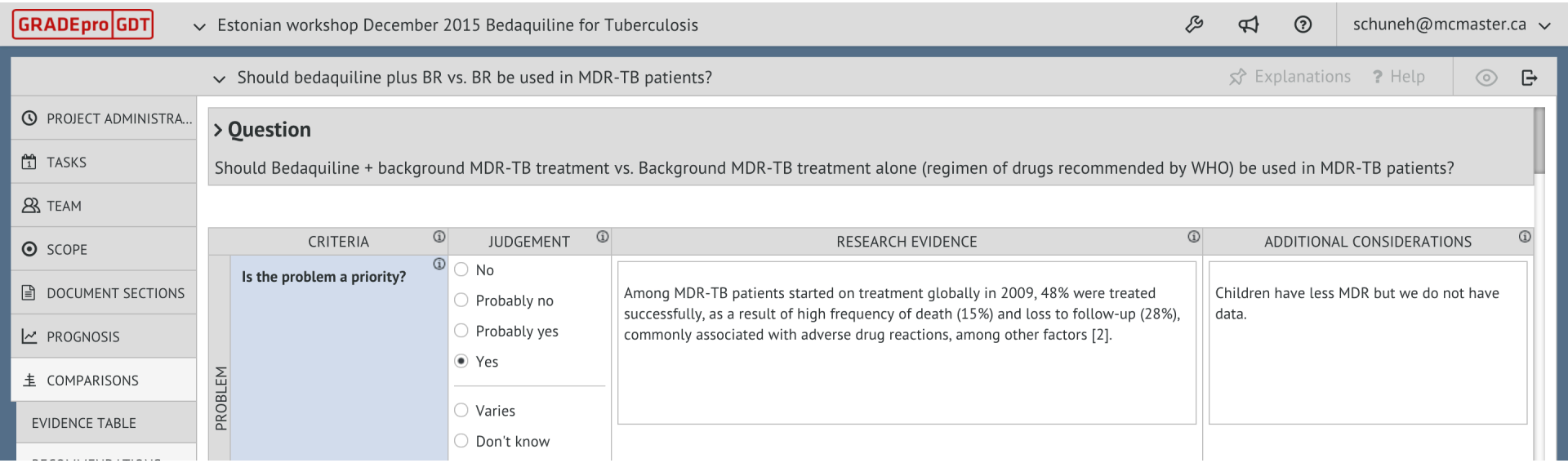
Holger J. Schünemann[a,b,c,*], Reem Mustafa[a,c,d], Jan Brozek[a,b,c], Nancy Santesso[a,c], Pablo Alonso-Coello[a,c,e], Gordon Guyatt[a,b,c], Rob Scholten[f], Miranda Langendam[c,g], Mariska M. Leeflang[g], Elie A. Akl[a,c,h], Jasvinder A. Singh[c,i], Joerg Meerpohl[c,j],

Development
GRADE Evidence to Decision (EtD) Frameworks

An iterative 5-year process:

- GRADE Working Group's approach to EtD
- Review of relevant literature and surveys
- Brain storming
- Feedback from stakeholders
- Application to examples (>100 recs) across health topics
- User testing

EtD frameworks



- ***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**

Neumann et al. Implementation Science (2016) 11:93
DOI 10.1186/s13012-016-0462-y

Implementation Science

RESEARCH Open Access

The GRADE evidence-to-decision framework: a report of its testing and application in 15 international guideline panels

Ignacio Neumann[1,2], Romina Brignardello-Petersen[1,3], Wojtek Wiercioch[1], Alonso Carrasco-Labra[1,3], Carlos Cuello[1], Elie Akl[4], Reem A. Mustafa[1,5], Waleed Al-Hazzani[1], Itziar Etxeandia-Ikobaltzeta[1,7], Maria Ximena Rojas[8], Maicon Falavigna[9], Nancy Santesso[1], Jan Brozek[1,6], Alfonso Iorio[1], Pablo Alonso-Coello[1,10] and Holger J. Schünemann[1,6*]

OPEN ACCESS Freely available online

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

Evidence to decision

- 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 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: 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*
	☐	☐			☑	☐

GRADE
DECIDE

Criteria	How the factor influences the direction and strength of a recommendation
Problem	The problem is determined by the importance and frequency of the health care issue that is addressed (burden of disease, prevalence or baseline risk). If the problem is of great importance a strong recommendation is more likely.
Values and preferences	Values and preferences or the importance of outcomes. This describes how important health outcomes are to those affected, how variable the importance is and if there is uncertainty about this.
Certainty in the evidence	The higher the certainty in the evidence the more likely is a strong recommendation.
Health benefits and harms and burden and their balance	This requires an evaluation of the absolute effects of both the benefits and harms and their importance. The greater the net benefit or net harm the more likely is a strong recommendation for or against the option.
Resource implications	This describes how resource intense an option is, if it is cost-effective and if there is incremental benefit. The more advantageous or clearly disadvantageous these resource implications are the more likely is a strong recommendation.
Equity	The greater the likelihood to reduce inequities or increase equity and the more accessible an option is, the more likely is a strong recommendation.
Acceptability	The greater the acceptability of an option to all or most stakeholders, the more likely is a strong recommendation.
Feasibility	The greater the feasibility of an option to all or most stakeholders, the more likely is a strong recommendation.

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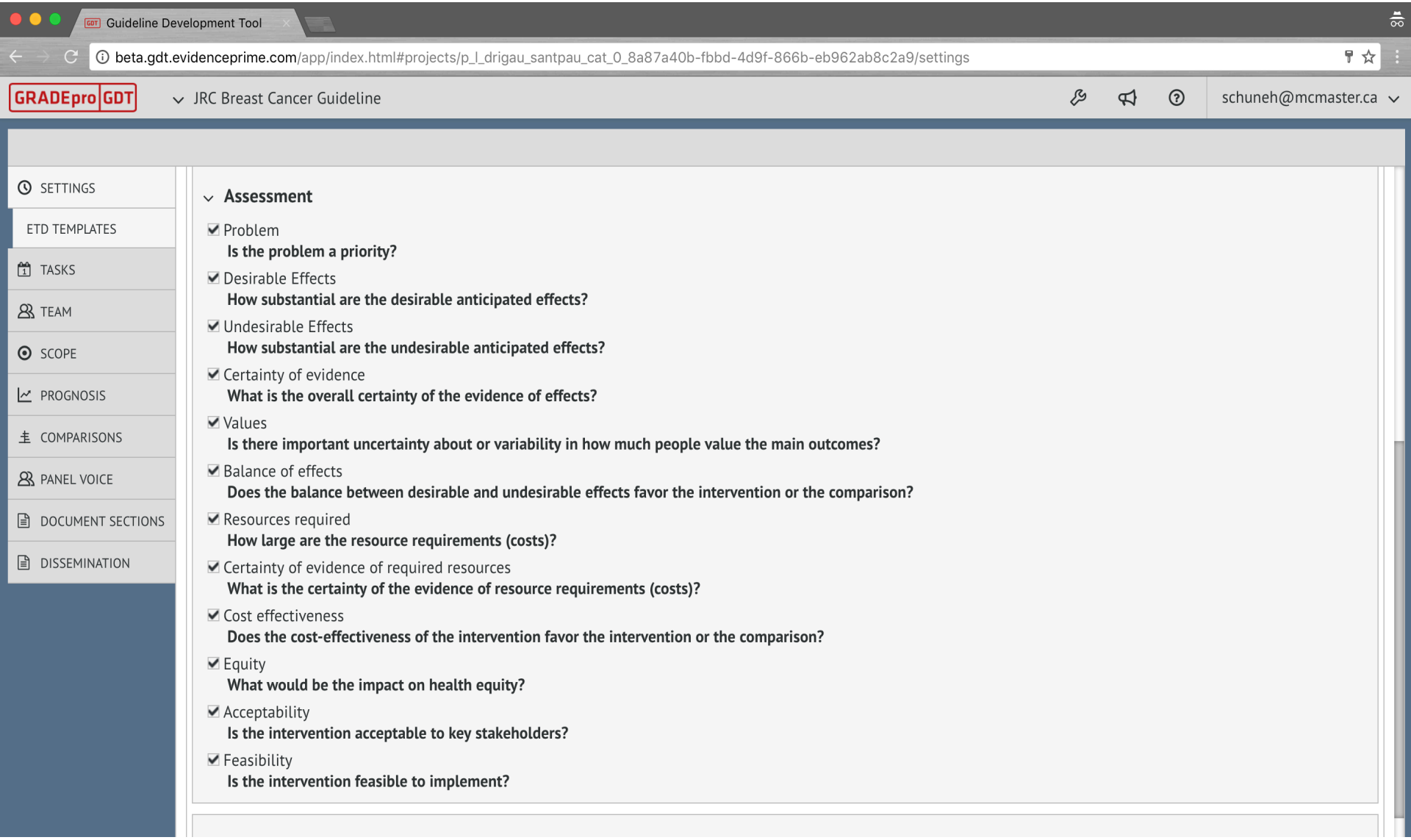

Guideline Development Tool
beta.gdt.evidenceprime.com/app/index.html#projects/p_l_drigau_santpau_cat_0_8a87a40b-fbbd-4d9f-866b-eb962ab8c2a9/settings
GRADEpro GDT
JRC Breast Cancer Guideline
schuneh@mcmaster.ca
SETTINGS
ETD TEMPLATES
TASKS
TEAM
SCOPE
PROGNOSIS
COMPARISONS
PANEL VOICE
DOCUMENT SECTIONS
DISSEMINATION
Assessment
Problem
Is the problem a priority?
Desirable Effects
How substantial are the desirable anticipated effects?
Undesirable Effects
How substantial are the undesirable anticipated effects?
Certainty of evidence
What is the overall certainty of the evidence of effects?
Values
Is there important uncertainty about or variability in how much people value the main outcomes?
Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?
Resources required
How large are the resource requirements (costs)?
Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?
Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?
Equity
What would be the impact on health equity?
Acceptability
Is the intervention acceptable to key stakeholders?
Feasibility
Is the intervention feasible to implement?

WHO recommendation on group antenatal care

- Antenatal care (ANC) conventionally involves one-on-one consultations. Group ANC integrates the usual health assessment with facilitated educational activities and peer support

Question: Should group antenatal care be recommended as an alternative to standard antenatal care?

- **Perspective:** Health systems perspective
- **Population:** All pregnant women
- **Aim:** To improve quality of antenatal care and the pregnancy experience
- **Option:** Group antenatal care
- **Comparison:** Standard (one-to-one) antenatal care
- **Main outcomes**: Positive pregnancy experience, maternal health outcomes, perinatal health outcomes

What matters to women receiving antenatal care?

- Qualitative evidence synthesis (Downe et al 2015)
- Shows that women across all cultural and sociodemographic contexts want a positive pregnancy experience

«Positive pregnancy experience»

Maintaining a healthy pregnancy (including preventing or treating risks, illness or death)

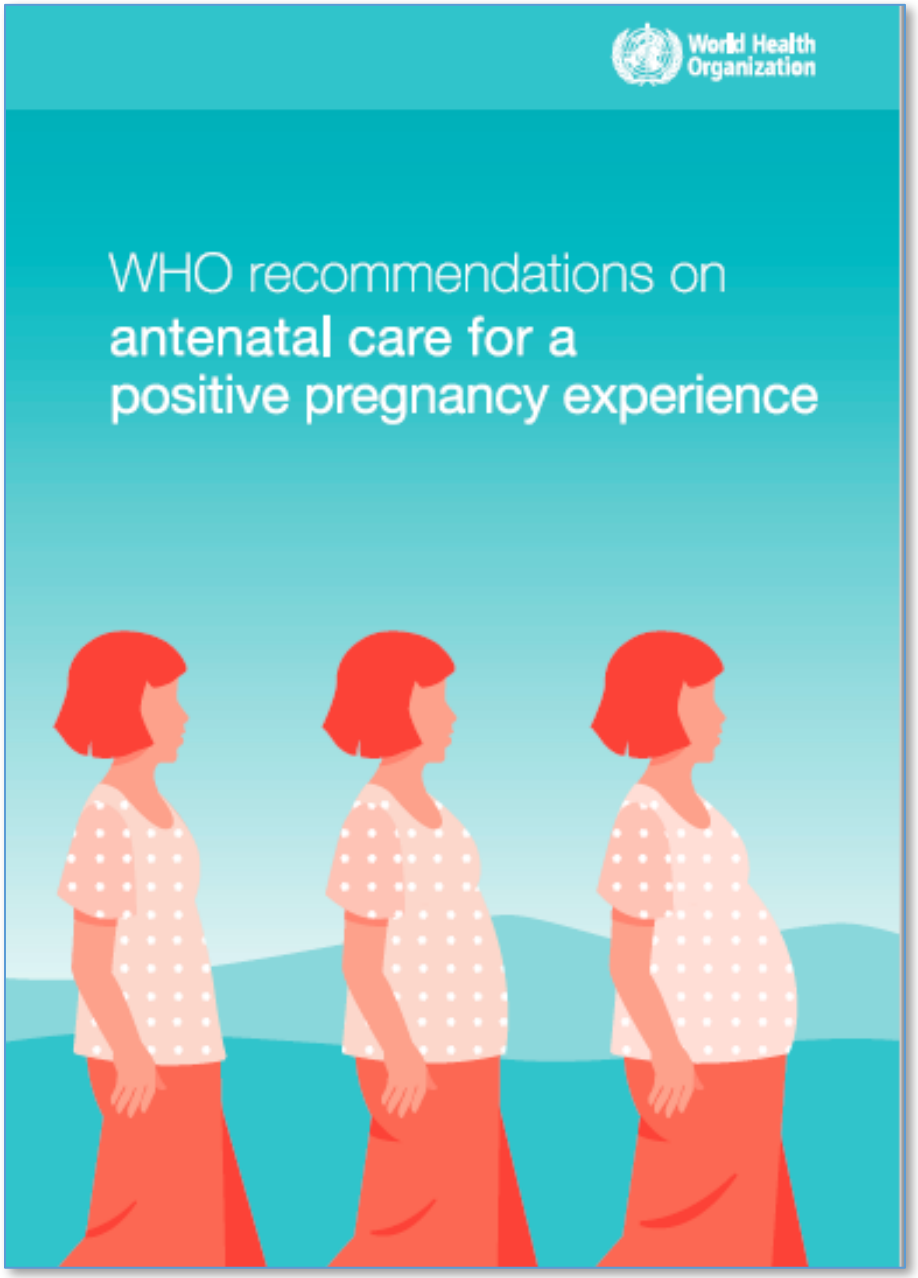
Having an effective transition to positive labour and birth

Achieving positive motherhood

Maintaining physical and sociocultural normality

Impact on guideline process

- Antenatal care not only viewed as a clinical process
- Acknowledgement of pregnancy as an important social phenomenon
- (However, design of trials and reviews rarely reflect this perspective)



What are the benefits and harms of the intervention?

Outcomes	Individual ANC	Group ANC	Certainty of the evidence (GRADE)	Comments
Preterm birth	**105 per 1000**	**79 per 1000** (60 to 105)	**Moderate**	Group ANC may reduce preterm birth. However, the CI includes no difference
Low birthweight	**89 per 1000**	**82 per 1000** (60 to 109)	**Moderate**	Group ANC probably has little or no effect on birth weight
Perinatal mortality	**21 per 1000**	**14 per 1000** (7 to 27)	**Low**	Group ANC may have little or no effect on perinatal mortality
Women's satisfaction			**Moderate**	Group ANC probably leads to higher satisfaction
Spontaneous vaginal birth	**606 per 1000**	**582 per 1000** (485 to 697)	**High**	Group ANC does not have an important effect on spontaneous vaginal birth

Catling et al, 2015

Judgement: Probably favours group antenatal care

What resources does the intervention require?

Group ANC	
Resource item	**Description**
Staff	At least two health care providers per group. Providers should speak the local language
Training	Staff to be trained in communication, facilitation and behaviour-change skills
Physical resources	• Training costs, including provision of training manuals (translated if necessary), and transport and subsistence of staff during training • A large, well-ventilated group space with movable chairs that can be arranged in a circle, and including an area that can be screened off for examinations • Automatic blood pressure monitors and scales for self-assessment • Session materials such as videos, picture cards, dolls, and educationally and culturally appropriate information booklets for women to take home • Music and refreshments (optional) • Other equipment as per usual ANC
Time to deliver the task	Sessions last 90-120 minutes
Supervision and monitoring	For a finite period after implementation, then as for usual ANC
Referral	As for usual ANC

Judgement: Neither favours this option or other options

Is the intervention acceptable?

Evidence from high-income settings:

- Most women enjoy the group format – use it to build socially supportive relationships (high confidence)
- Most women appreciate the additional time (high confidence), but some women don't attend because of it (moderate confidence)

Downe et al, 2015

- Some women have reservations about the lack of privacy during the group sessions, particularly during physical examinations (low confidence)
- Providers find group sessions to be enjoyable and a more efficient use of their time (moderate confidence)
- No evidence from low or middle-income settings. Indirect evidence suggests that in rural areas of some LMICs where traditional beliefs restrict pregnancy exposure, the group approach may be inappropriate (moderate confidence)

Judgement: Probably favours group antenatal care

Is the intervention feasible to implement?

- Providers view the facilitative component of group antenatal care as a skill that requires additional training and provider commitment (*moderate confidence in the evidence*)

- Some providers also feel that clinics need to be better equipped to deliver group sessions, i.e. clinics need to have large enough rooms with adequate seating (*moderate confidence in the evidence*)

Downe et al, 2015

Judgement: Neither favours this option or other options

What did the WHO recommend?

We suggest considering the option only in specific circumstances

Group antenatal care should be offered as an alternative to standard (individual) antenatal care for pregnant women depending on a woman's preferences and provided that the infrastructure and resources for delivery of group care are available

Implementation considerations

(Based on the qualitative evidence syntheses)

The following should be considered when implementing group antenatal care:

- Group antenatal care may take longer than individual antenatal care, and this may pose practical problems for some women in terms of work and childcare. Healthcare providers should be able to offer a variety of time slots for group sessions (morning, afternoon, evening) and should consider making individual care available as well (especially for women with complications in pregnancy)
- Healthcare providers and their supervisors need to receive appropriate initial and refresher/booster training in group facilitation and communication
- Pre-service training institutions and professional bodies should also be informed and involved so that training curricula and supervision guidelines are updated
- Healthcare providers need to be have appropriate facilities to deal with group sessions, including access to large, well-ventilated rooms, or sheltered spaces and adequate seating
- Women's need for privacy should be considered. A private space should be made available for physical examinations, and opportunities should be given for private conversations
- Etc.

Research priorities

(Topics with lack of evidence or low / very low GRADE and GRADE-CERQual assessments)

More research is needed:

- To determine the optimal, most acceptable, and feasible group size and frequency of group ANC visits in a variety of settings
- To assess the effect of group ANC and FANC on maternal and perinatal outcomes, including pre-eclampsia, anaemia, excessive gestational weight gain, gestational diabetes mellitus, infections, caesarean section, preterm birth, low birth weight, maternal and perinatal mortality, and coverage outcomes (ANC visits and facility delivery)
- To assess the acceptability and feasibility of group FANC in various settings
- To assess whether group FANC should also include high-risk women, in addition to such women receiving specialist care, so that high-risk women don't miss out on the communication and social support aspects of ANC
- To assess the cost-effectiveness of group FANC in low- and middle-income settings
- To assess the effects of group FANC on health literacy and other equity-related outcomes
- To assess effects of group ANC on other healthy behaviours, such as breastfeeding initiation and postnatal contraception

ASH Heparin in Cancer

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

Interim policy guidance

World Health Organization

WHO 2013

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…		Absolute		

Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]

1 "phase 2" RCT evaluating cure

59 events

132 patie…

120 weeks

RR = 1.81

fo…

26/100 more patients cured

Mortality up to end of study at 120 weeks (C208 Sta…

Mortality – SAE?

1… events in
…) patients
1…) 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.
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).

WHO, 2013

Participants: *MDR TB patients*
Intervention: *bedaquiline + background MDR TB treatment*
Comparison: *background MDR TB treatment alone*

▸ About this summary

Add or remove columns: ⇕ Visual overview

Outcome	Plain language summary	Absolute Effect: Without bedaquiline	Absolute Effect: With bedaquiline	Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
Cured by end of study Follow-up: 120 weeks	*Bedaquiline may increase the number of patients cured.*	32 per 100	58 per 100	RR 1.81 (1.26 to 2.31) Based on data from 132 patients in 1 study	⊕⊕◯◯ Low
		Difference 26 more per 100 patients (95% CI: 8 to 42 more per 100 patients)			
Serious adverse events Follow-up: 24 week treatment phase	*It is uncertain whether bedaquiline increases the number of patients who have adverse effects.*	2 per 100	7 per 100	RR 3.6 (0.77 to 14.00) Based on data from 207 patients in 2 studies	⊕◯◯◯ Very low
		Difference 5 more per 100 patients (95% CI: 0 to 25 more per 100 patients)			
Mortality Follow-up: 120 weeks	*It is uncertain whether bedaquiline increases the number of patients who die.*	3 per 100	13 per 100	RR 9.23 (1.20 to 72.95) Based on data from 160 patients in 1 study	⊕◯◯◯ Very low
		Difference 10 more per 100 patients (95% CI: 0 to 53 more per 100 patients)			

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Question

Should Bedaquiline + background MDR-TB treatment vs. Background MDR-TB treatment alone (regimen of drugs recommended by WHO) be used in Multidrug-resistant tuberculosis (MDR-TB) ?

Recommendations preview

Assessment

	CRITERIA	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	○ No ○ Probably no ○ Probably yes ◉ Yes ○ Varies ○ Don't know Detailed judgements	Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors [2].	
	How substantial are the desirable anticipated effects?	○ Trivial ○ Small ○ Moderate ◉ Large ○ Varies ○ Don't know Detailed judgements	Summary of findings: Bedaquiline for multidrug-resistant tuberculosis **Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO) in MDR-TB patients**	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with Background MDR-TB treatment alone (regimen of drugs recommended by WHO)	Risk with Bedaquiline + background MDR-TB treatment			
Subjects cured by	**Study population**		**RR 1.81**	132	⨁⨁◯◯

DESIRABLE EFFECTS

- ○ Moderate
- ◉ Large
- ○ Varies
- ○ Don't know

Detailed judgements

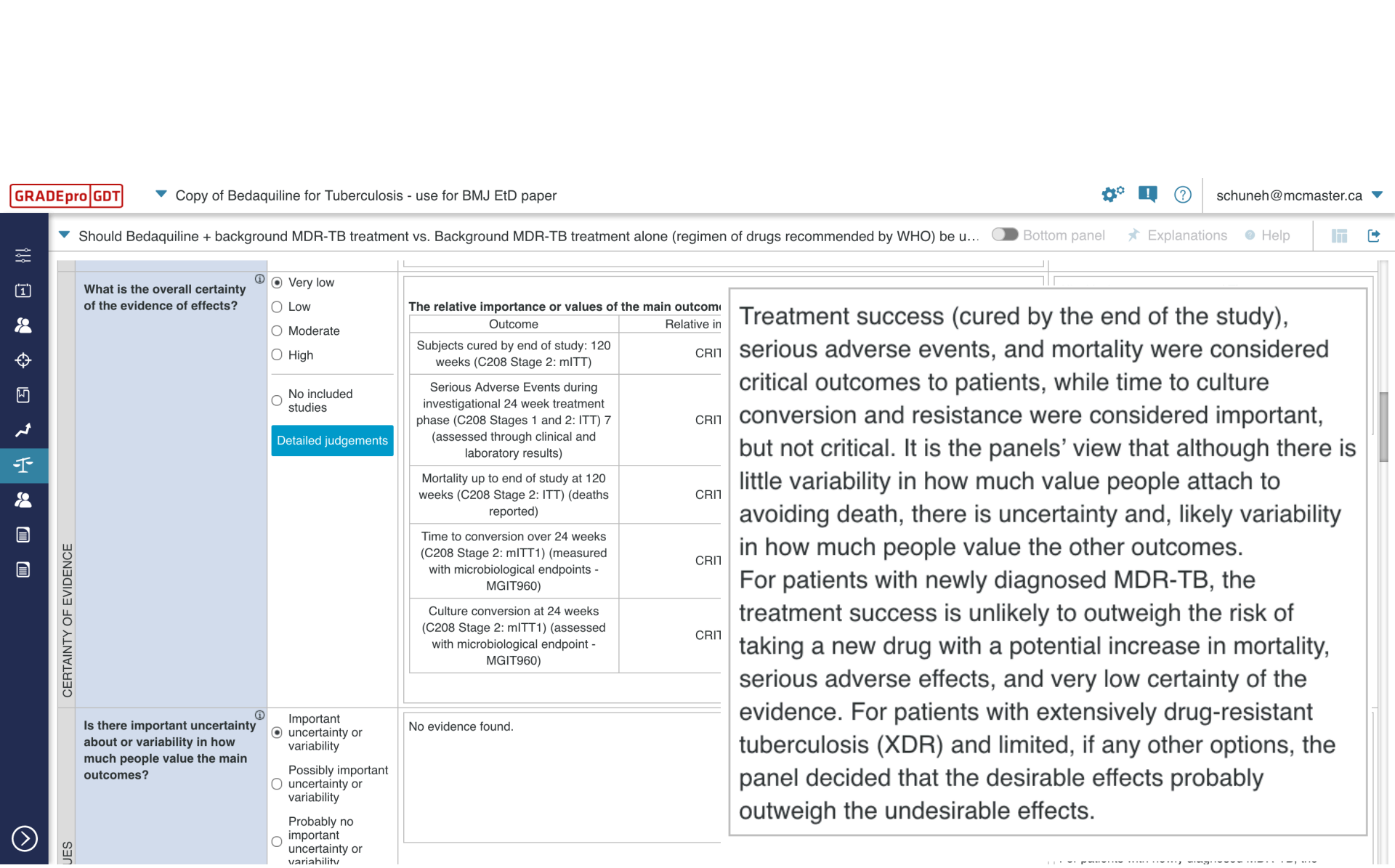
Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO) in MDR-TB patients

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with Background MDR-TB treatment alone (regimen of drugs recommended by WHO)	Risk with Bedaquiline + background MDR-TB treatment			
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)[1,2]	**Study population**		**RR 1.81** (1.26 to 2.31)[3,6]	132 (1 RCT)[1,3]	⨁⨁◯◯ LOW[4,5]
	32 per 100[1]	**58 per 100** (40 to 74)[1]			
Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)	**Study population**		**RR 3.60** (0.77 to 14.00)	207 (2 RCTs)[7,9]	⨁◯◯◯ VERY LOW[5,8]
	2 per 100	**7 per 100** (1 to 27)[9]			
Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)	**Study population**		**RR 9.23** (1.20 to 72.95)[12,13]	160 (1 RCT)[10]	⨁◯◯◯ VERY LOW[3,11]
	1 per 100[10]	**11 per 100** (1 to 90)[10]			
Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)	**Study population**		not estimable	(1 RCT)[14]	⨁⨁◯◯ LOW[4,5,15]
	0 per 100	**NaN per 100** (NaN to NaN)			
Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)	**Study population**		**RR 1.37** (1.10 to 1.77)[17]	132 (1 RCT)[1,16]	⨁⨁◯◯ LOW[4,5,15]
	58 per 100[1]	**79 per 100** (63 to 100)[1]			
Acquired resistance to	**Study population**		**RR 0.39**	37	⨁◯◯◯

How substantial are the undesirable anticipated effects?

- ◉ Large
- ○ Moderate
- ○ Small
- ○ Trivial
- ○ Varies
- ○ Don't know

Detailed judgements


GRADEpro GDT
Copy of Bedaquiline for Tuberculosis - use for BMJ EtD paper
schuneh@mcmaster.ca
Should Bedaquiline + background MDR-TB treatment vs. Background MDR-TB treatment alone (regimen of drugs recommended by WHO) be u…
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CERTAINTY OF EVIDENCE
What is the overall certainty of the evidence of effects?
Very low
Low
Moderate
High
No included studies
Detailed judgements
The relative importance or values of the main outcom
Outcome
Relative in
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)
CRIT
Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)
CRIT
Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)
CRIT
Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)
CRIT
Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)
CRIT
Treatment success (cured by the end of the study), serious adverse events, and mortality were considered critical outcomes to patients, while time to culture conversion and resistance were considered important, but not critical. It is the panels' view that although there is little variability in how much value people attach to avoiding death, there is uncertainty and, likely variability in how much people value the other outcomes.
For patients with newly diagnosed MDR-TB, the treatment success is unlikely to outweigh the risk of taking a new drug with a potential increase in mortality, serious adverse effects, and very low certainty of the evidence. For patients with extensively drug-resistant tuberculosis (XDR) and limited, if any other options, the panel decided that the desirable effects probably outweigh the undesirable effects.
Is there important uncertainty about or variability in how much people value the main outcomes?
Important uncertainty or variability
Possibly important uncertainty or variability
Probably no important uncertainty or variability
No evidence found.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ◉ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know Detailed judgements	See evidence profile above	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?**	○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ◉ Varies ○ Don't know Detailed judgements	Cost data for the base case in each country were sourced from published studies [1], with additional supplementary data provided by study authors. For the primary estimates for the unit cost per patient treatment with Bedaquiline, a regimen cost of US $900 (for Global Fund Eligible countries) and US $3000 (for all other countries) was used for a full course of bedaquiline based on estimates from Janssen. In addition the costs of four electro-cardiograms were added. To estimate the possible cost savings from a shortened course with bedaquiline, the costs of an intensive phase of six months were estimated. Eight month intensive phase drug costs were adjusted to take into account reductions in hospitalization and required length of second-line parenteral agents (injectable anti-tuberculosis drugs). Where hospitalization was not used extensively in the intensive phase of treatment (Peru and Nepal), a reduction was made in the cost of clinic visits. All other costs (programme management, testing costs etc.) were conservatively assumed to remain the same as the non-shortened bedaquiline regimen.	

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?**	○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ◉ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies Detailed judgements	Modelling of the incremental cost-effectiveness of adding bedaquiline to WHO recommended MDR-TB regimens was conducted by an independent consultant contracted by WHO for review by the expert group [2]. The model assumed that bedaquiline would be added to treatment for all patients starting MDR-TB treatment. Several scenarios were explored to appraise the cost-effectiveness of bedaquiline in these settings. Under the model assumptions, the bedaquiline-containing regimens were assessed as relatively cost-effective in most settings, but results were ambiguous in low-income settings, and highly dependent on the assumptions made about the generalizability of trial results to routine settings.	There are variations of cost effectiveness across settings based on data and assumptions used in the model – that may not reflect real life situations. In addition, there were a series of limitations in the model being used for analysis of cost-effectiveness (e.g. no accounting of serious adverse events, no accounting for effect on transmission, etc.) As the recommendation of the expert group is to use bedaquiline for only selected sub-groups of the full MDR-TB patient population (as opposed to all patients with MDR-TB that were considered in the cost-effectiveness analysis), the cost-effectiveness model needs to be further refined such that results are available for these sub-groups specifically.
EQUITY	**What would be the impact on health equity?**	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ◉ Don't know Detailed judgements	No research evidence found	It is difficult to assess whether bedaquiline would have an impact on equity because of uncertainty about affordability and its effects. If it is effective and is not available to some people because it is not affordable or accessible, this would reduce equity. Lack of access to monitoring might also reduce equity. On the other, it is the panel's view that, to the extent that the desirable effects of bedaquiline outweigh the undesirable effects, ensuring that it is accessible to XDR patients could increase equity.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?**	○ No ○ Probably no ○ Probably yes ○ Yes ◉ Varies ○ Don't know Detailed judgements	No evidence found.	Some health care providers might be reluctant to treat patients with bedaquiline given the very low certainty of the evidence and possibly increased mortality and serious adverse effects. On the other hand, the panel decided that some health care providers might be reluctant not to treat patients with such a bad prognosis.
FEASIBILITY	**Is the intervention feasible to implement?**	○ No ○ Probably no ○ Probably yes ○ Yes ◉ Varies ○ Don't know Detailed judgements	No evidence found.	Costs and local regulatory constraints might be barriers to scaling up the use of bedaquiline. The view of the panels is that clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place.

BALANCE OF EFFECTS	Favors the comparison	Probably favors the...	Does not favor either the...	**Probably favors the...**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and...	Moderate savings	Large savings	**Varies**	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High		No included studies		
COST EFFECTIVENESS	Favors the comparison	Probably favors the...	Does not favor either the...	**Probably favors the...**	Favors the intervention	Varies	No...	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusions

Should Bedaquiline + background MDR-TB treatment vs. Background MDR-TB treatment alone (regimen of drugs recommended by WHO) be used in Multidrug-resistant tuberculosis (MDR-TB) ?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	◉	○

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Conclusions

Should Bedaquiline + background MDR-TB treatment vs. Background MDR-TB treatment alone (regimen of drugs recommended by WHO) be used in MDR-TB patients?

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	◉	○

Recommendation

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

In addition:

- A duly informed decision making-process by patients should be followed. Patient should know the risk.
- What dose? Lower dose to lower the risk of bedaquiline
- If patient is already on QT prolongating drugs then possible avoid use. E.g. PLHIV. Need to monitor ECG in these patients.
- Do not apply to children - risk are too high.

Cancel | Apply

Justification

Overall justification

Detailed justification

Desirable Effects
2.5 x higher probability of being cured than dying with the intervention (for different reasons).

Undesirable Effects