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Department of Health Research Methods, Evidence and Impact
McMaster University

December 11, 2018 | NAS

GRADE Evidence-to-Decision Frameworks

for Considering Mechanistic Data with Animal and Human Data to Support Evidence Synthesis and Integration

Disclosures

Cochrane Canada - Director

GRADE working group Co-Chair

Guideline International Network - committees

No direct financial COI – reimbursement travel

Views expressed my own

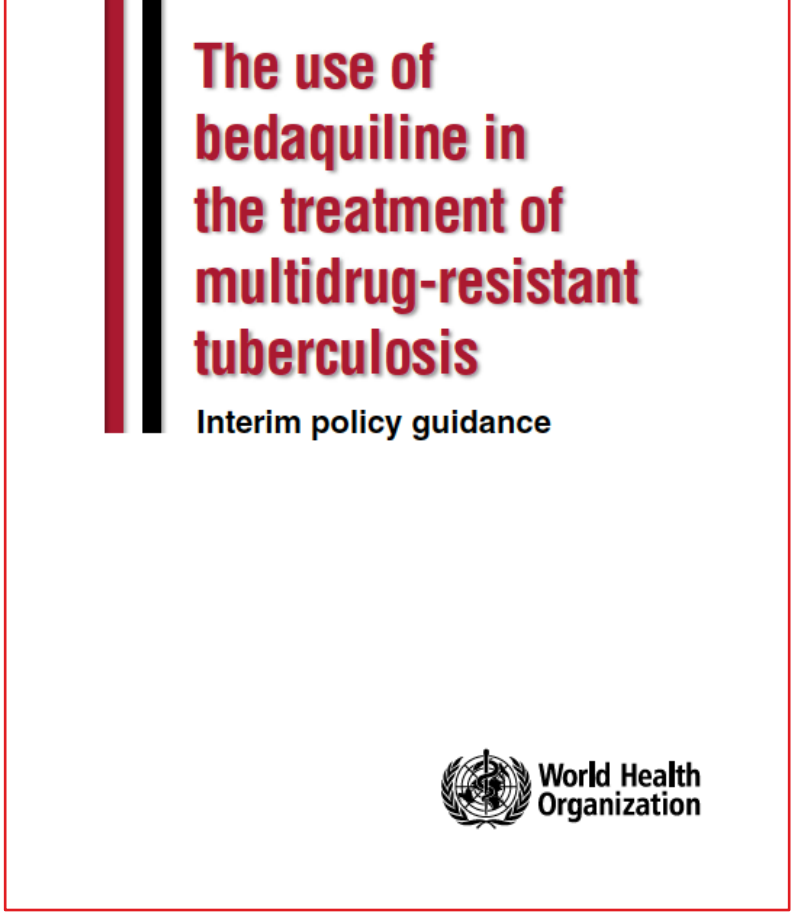
Today

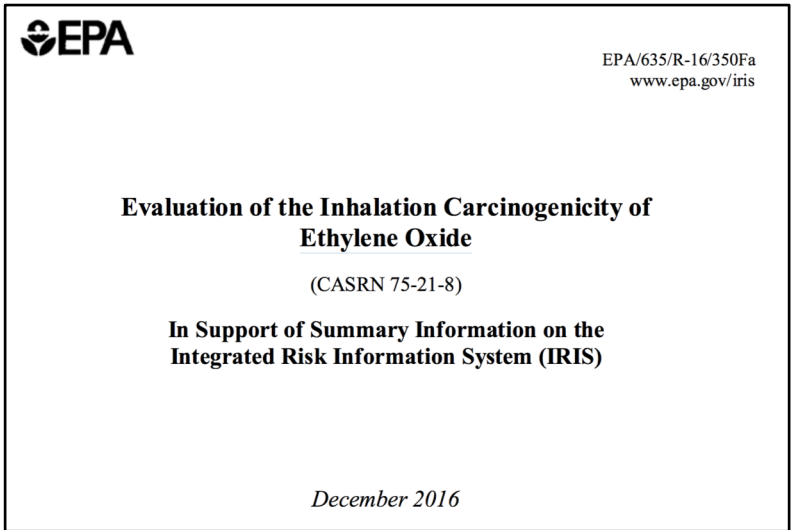
- Background on Evidence to Decision (EtD) Frameworks
- Making recommendation and decisions
- Application in public health and health policy context

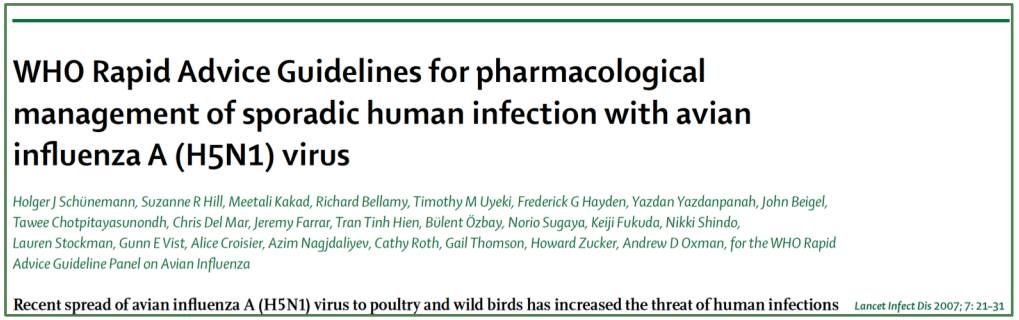
Examples

WHO policy documents

EPA - Evaluation of the Inhalation of Ethylene Oxide







Why do Systematic Reviews?

The questions we address serve to influence or make decisions.

Etiology

PECO

A sensible question

Population: People

Exposures: Ethylene Oxide
Comparison: no, different levels of, exact cut offs of Ethylene Oxide

Outcomes: different types of cancer

PECO

Decisions

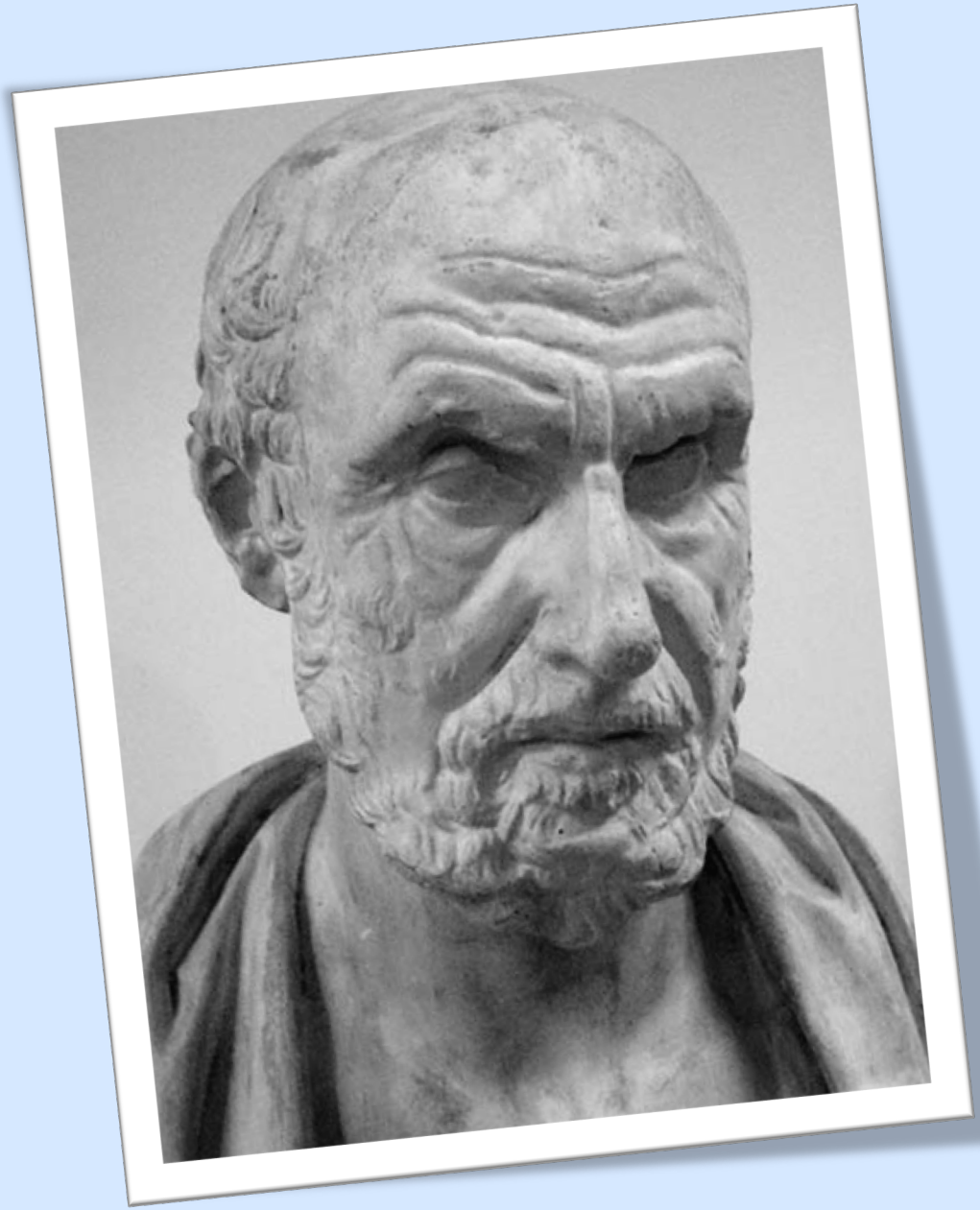
Population: People

Intervention: Regulation to ban/reduce to certain level

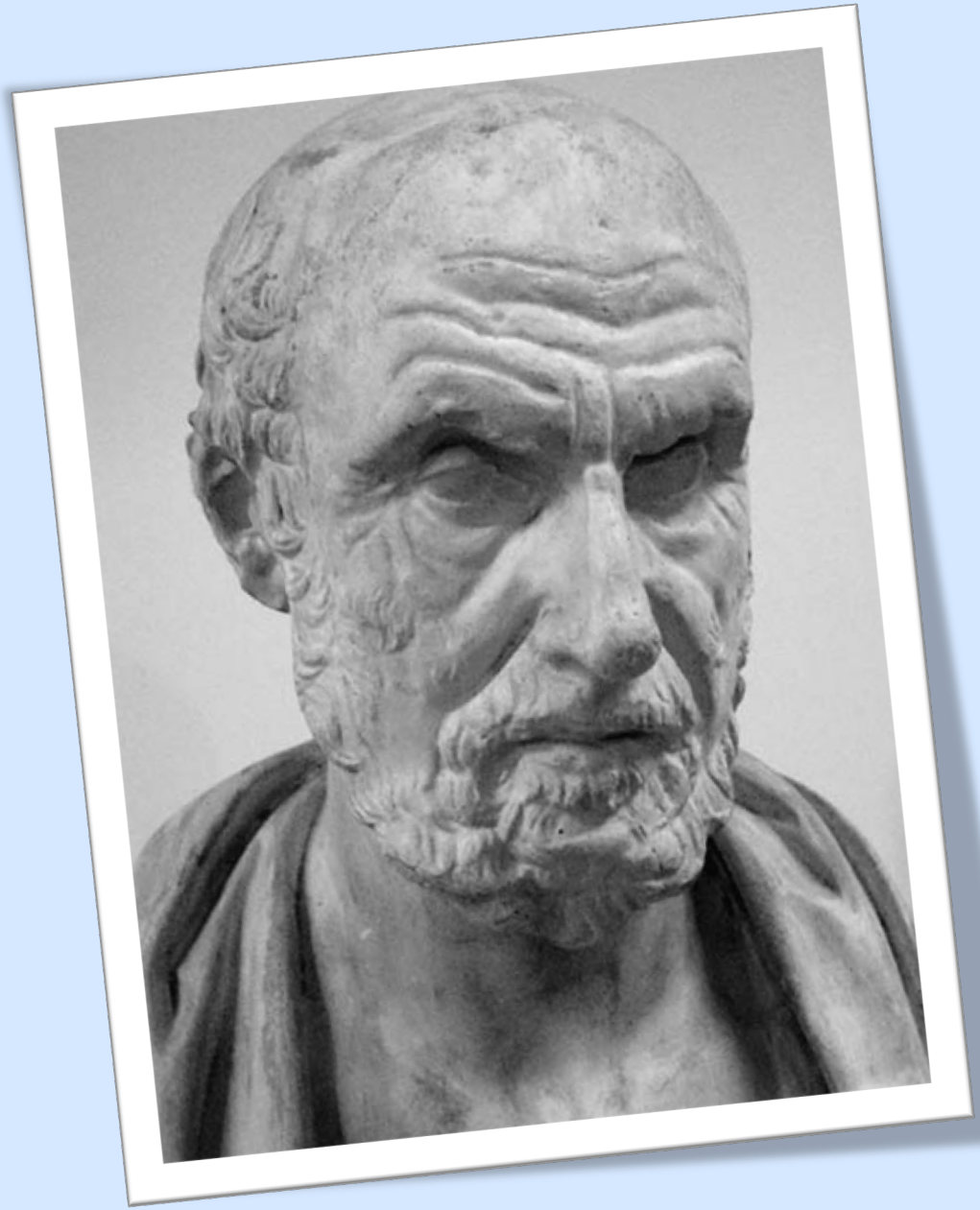
Comparison: no regulation

Outcomes: cancer, road safety (ethylene glycol), surgical infections

PICO



do no harm



do no net harm

Schünemann, 2011

Benefits
Importance
Low co$t
Doable

Harms
Importance
High co$$$t
~~Doable~~


ARE YOU
SURE?

Development of
GRADE Evidence to Decision (EtD) Frameworks

An iterative 5-year process – EU funded:

GRADE Working Group's approach to EtD

Review of relevant literature and surveys

Feedback from stakeholders

Application to examples (>100 recs) across health topics

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

GRADE

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]

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

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 Br
Pablo Alonso-Coello[a,c,e], Gordon Guyatt[a,b,c], Rob Scholt
Mariska M. Leeflang[g], Elie A. Akl[a,c,h], Jasvinder A. S
na

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

Implementation Science

doi:10.1017/S0266462317000447

Methods

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*]

GRADE EVIDENCE TO DECISION (EtD) FRAMEWORK FOR COVERAGE DECISIONS

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Local Health Authority ASL Roma 1, Rome

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Marina Davoli
Department of Epidemiology, Lazio Regional Health Service - ASL Roma 1

the GRADE Working Group

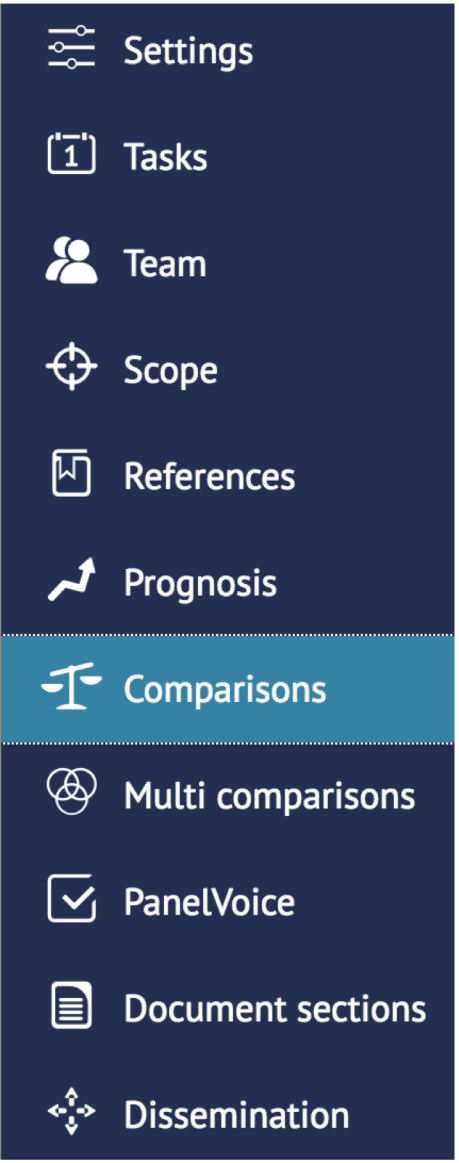
GRADE Evidence to Decision (EtD) framework

Can help and decision makers move from evidence to a recommendation or decision by:

- Informing judgements about the pros and cons of each option
- 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:
  - Clinical and public health
  - Policy making
  - Health systems
  - Coverage decisions

GRADE

interactive Evidence to Decision Frameworks



Question

- Details – PICO – perspective (population, system, etc)
- Subgroups
- Background

Assessment

- Criteria
- Judgements
- Research evidence (HTA and Systematic Reviews)
- Additional considerations

Conclusions

- Type of decision - recommendation
- Justification
- Implementation considerations - monitoring and evaluation
- Research considerations

Presentation

- Guideline group meetings & informing coverage decisions
- Database of decision frameworks
- Interactive Decision Aids (iDeAs), apps

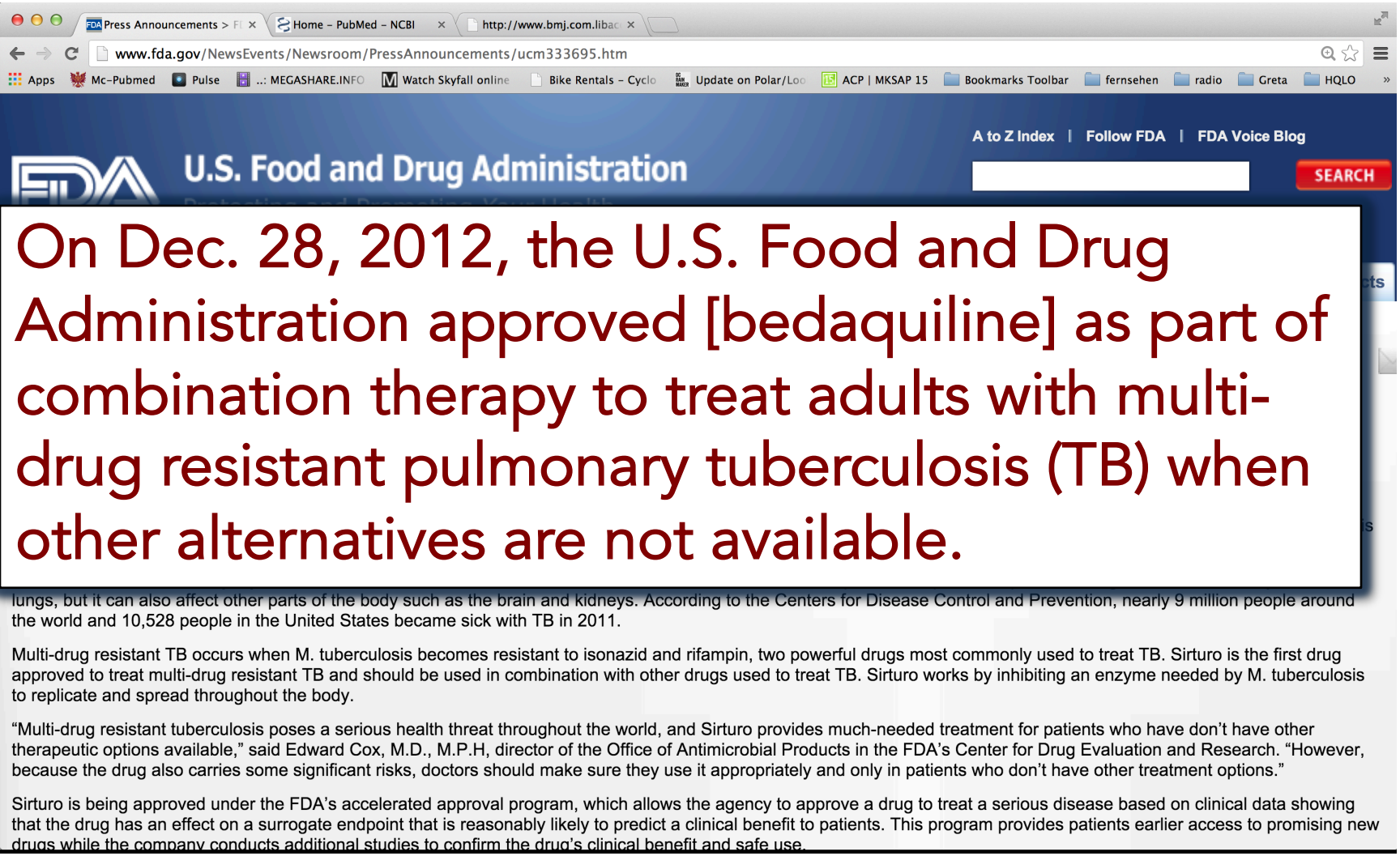
BMJ, JCE, IJHTA, HARPS, 2016-18

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

Interim policy guidance

World Health Organization

WHO 2013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http://www.bmj.com.liba
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Pulse
..: MEGASHARE.INFO
Watch Skyfall online
Bike Rentals - Cyclo
Update on Polar/Loo
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U.S. Food and Drug Administration
SEARCH
On Dec. 28, 2012, the U.S. Food and Drug Administration approved [bedaquiline] as part of combination therapy to treat adults with multi-drug resistant pulmonary tuberculosis (TB) when other alternatives are not available.
lungs, but it can also affect other parts of the body such as the brain and kidneys. According to the Centers for Disease Control and Prevention, nearly 9 million people around the world and 10,528 people in the United States became sick with TB in 2011.
Multi-drug resistant TB occurs when M. tuberculosis becomes resistant to isonazid and rifampin, two powerful drugs most commonly used to treat TB. Sirturo is the first drug approved to treat multi-drug resistant TB and should be used in combination with other drugs used to treat TB. Sirturo works by inhibiting an enzyme needed by M. tuberculosis to replicate and spread throughout the body.
“Multi-drug resistant tuberculosis poses a serious health threat throughout the world, and Sirturo provides much-needed treatment for patients who have don’t have other therapeutic options available,” said Edward Cox, M.D., M.P.H, director of the Office of Antimicrobial Products in the FDA’s Center for Drug Evaluation and Research. “However, because the drug also carries some significant risks, doctors should make sure they use it appropriately and only in patients who don’t have other treatment options.”
Sirturo is being approved under the FDA’s accelerated approval program, which allows the agency to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. This program provides patients earlier access to promising new drugs while the company conducts additional studies to confirm the drug’s clinical benefit and safe use.

World Health Organization

provides TB diagnosis and treatment guidelines

new TB pharmaceuticals developed

demand from country programs, funders, patients, policy makers

new policy guideline for bedaquiline

- independent of other decisions

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Related articles

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

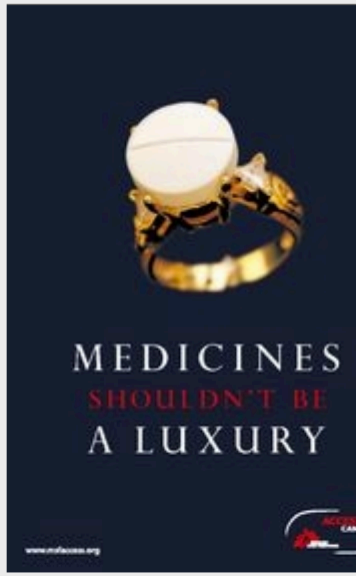
First new tuberculosis drug for 50 years – works on drug-resistant forms of the disease

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



www.citizen.org/hrg2088

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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

» Drug, Devices, and Supplements
» Physician Accountability
» Consumer Product Safety
» Worker Safety
» Health Care Delivery
» Auto and Truck Safety
» Global Access to Medicines
» Infant Formula Marketing

Evidence profiles

Question and source of evidence (systematic review)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to BR	BR alone	Relative (95%CI)	Absolute		
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]												
1[3]	randomized trials	no serious risk of bias[4]	no serious inconsistency	serious[5]	serious[5]	none	38/66[1] (57.6%)	21/66[1] (31.8%)	RR 1.81 (1.26 to 2.31)[3,6]	26 more per 100 (from 8 more to 42 more)	++OO Low	Critical
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)	5 more per 100 (from 0 to 25 more)	+OOO Very Low	Critical
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.
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Question: In MDR-TB patients, does the addition of a bedaquiline to a background regimen based on WHO recommendations safely improve patient outcomes?

Bibliography: 1. Janssen Pharmaceutical Companies, 2012. TMC207 (bedaquiline) treatment of patients with MDR-TB (NdA 204–384). Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 (document available for public disclosure without redaction). 2. US-FDA AIDAC Meeting 28 Nov 2012. Slide presentations by Janssen R&D; Slide presentations by US-FDA. (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm).

Population, intervention, comparator, outcomes

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Outcomes							**Effect estimates**					
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Outcomes

Effect estimates

Methods and evaluation

Certainty/quality by outcome:
- High
- Moderate
- Low
- Very low

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Criteria

Problem/priority?

Benefits & harms of the options

Certainty of evidence

Values

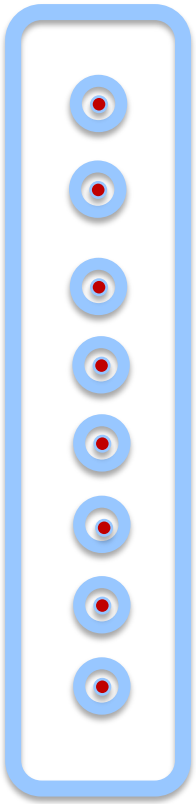
Resource use

Equity

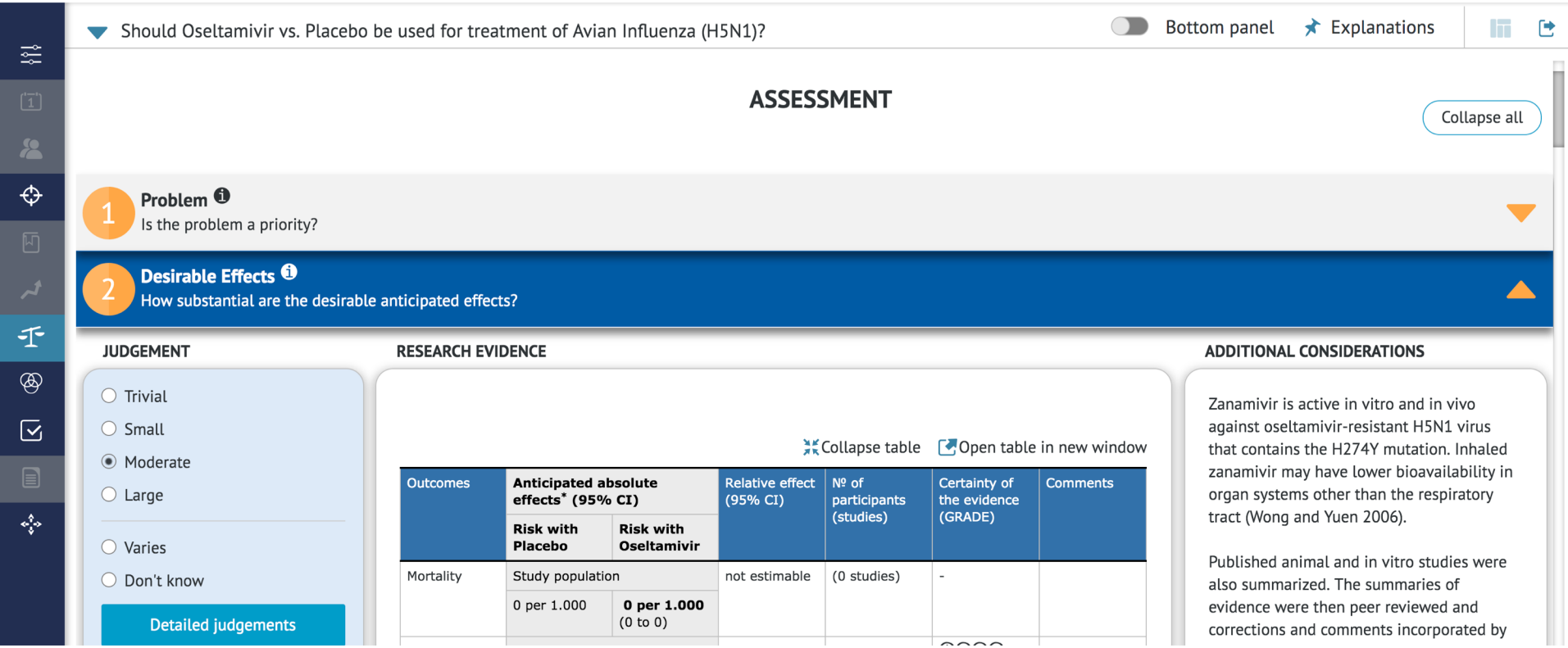
Acceptability

Feasibility

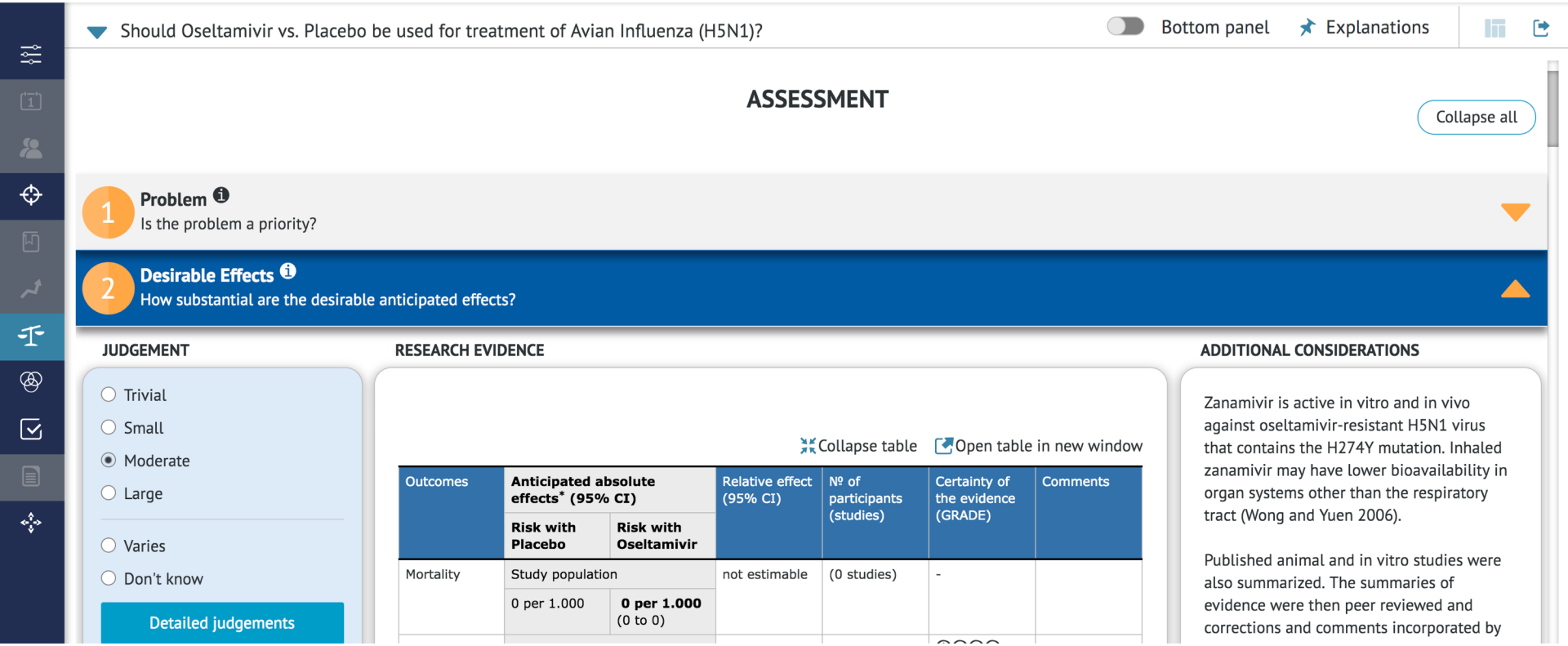
Evidence from Systematic Reviews



EtD frameworks

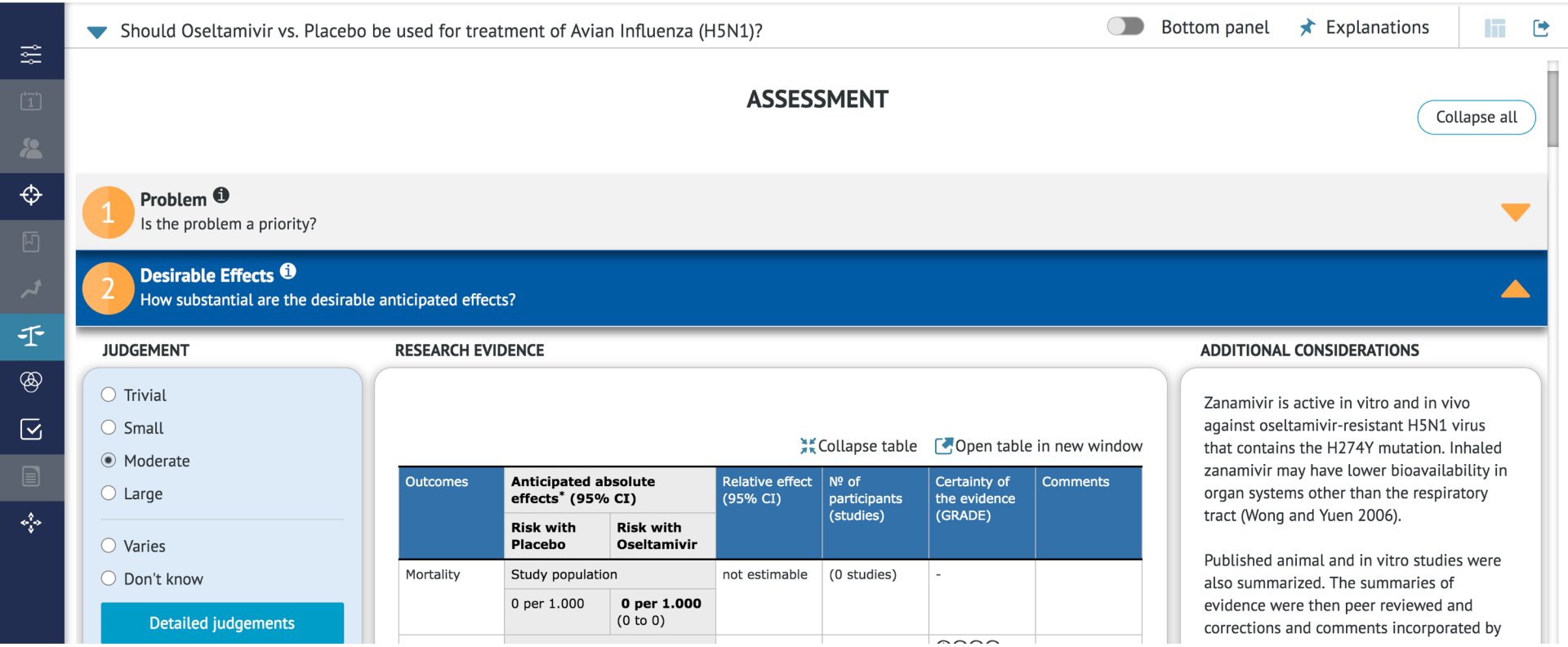


Discuss


Should Oseltamivir vs. Placebo be used for treatment of Avian Influenza (H5N1)?
Bottom panel
Explanations
ASSESSMENT
Collapse all
1
Problem
Is the problem a priority?
2
Desirable Effects
How substantial are the desirable anticipated effects?
JUDGEMENT
Trivial
Small
Moderate
Large
Varies
Don't know
Detailed judgements
RESEARCH EVIDENCE
Collapse table
Open table in new window
Outcomes
Anticipated absolute effects* (95% CI)
Risk with Placebo
Risk with Oseltamivir
Relative effect (95% CI)
№ of participants (studies)
Certainty of the evidence (GRADE)
Comments
Mortality
Study population
not estimable
(0 studies)
-
0 per 1.000
0 per 1.000 (0 to 0)
ADDITIONAL CONSIDERATIONS
Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation. Inhaled zanamivir may have lower bioavailability in organ systems other than the respiratory tract (Wong and Yuen 2006).
Published animal and in vitro studies were also summarized. The summaries of evidence were then peer reviewed and corrections and comments incorporated by

Discuss

Add


Should Oseltamivir vs. Placebo be used for treatment of Avian Influenza (H5N1)?
Bottom panel
Explanations
ASSESSMENT
Collapse all
1 Problem
Is the problem a priority?
2 Desirable Effects
How substantial are the desirable anticipated effects?
JUDGEMENT
Trivial
Small
Moderate
Large
Varies
Don't know
Detailed judgements
RESEARCH EVIDENCE
Collapse table
Open table in new window
Outcomes
Anticipated absolute effects* (95% CI)
Risk with Placebo
Risk with Oseltamivir
Relative effect (95% CI)
№ of participants (studies)
Certainty of the evidence (GRADE)
Comments
Mortality
Study population
not estimable
(0 studies)
-
0 per 1.000
0 per 1.000 (0 to 0)
ADDITIONAL CONSIDERATIONS
Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation. Inhaled zanamivir may have lower bioavailability in organ systems other than the respiratory tract (Wong and Yuen 2006).
Published animal and in vitro studies were also summarized. The summaries of evidence were then peer reviewed and corrections and comments incorporated by

Judge

No COI

Bedaquiline for MDR TB

1 **Problem**
Is the problem a priority?

JUDGEMENT

- ○ No
- ○ Probably no
- ○ Probably yes
- ◉ Yes
- ○ Varies
- ○ Don't know

Detailed judgements

RESEARCH EVIDENCE

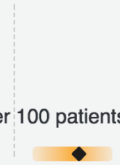
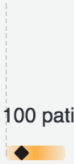
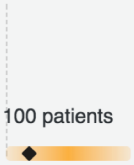
Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors [2].

2 **Desirable Effects**
How substantial are the desirable anticipated effects?

3 **Undesirable Effects**
How substantial are the undesirable anticipated effects?

4 **Certainty of evidence**
What is the overall certainty of the evidence of effects?

Plain language statements OFF | Absolute effect ON | Relative effect ON | Visual overview ON

Outcomes	Absolute Effect: Without Bedaquiline + background MDR-TB treatment	Absolute Effect: With Bedaquiline + background MDR-TB treatment	Differences in outcomes	Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence GRADE
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) Follow-up: 0 ◉ Study population ○ Moderate	32 per 100	58 per 100 Difference: 26 more per 100 patients (95% CI: 8 to 42 more per 100 patients) Based on data from 132 patients in 1 study		**RR 1.81** (1.26 to 2.31)	⨁⨁◯◯ Low
Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results) Follow-up: 0	2 per 100	7 per 100 Difference: 5 more per 100 patients (95% CI: 0 to 25 more per 100 patients) Based on data from 207 patients in 2 studies		**RR 3.6** (0.77 to 14)	⨁◯◯◯ Very low
Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported) Follow-up: 0	1 per 100	9 per 100 Difference: 8 more per 100 patients (95% CI: 0 to 53 more per 100 patients) Based on data from 160 patients in 1 study		**RR 9.23** (1.2 to 72.95)	⨁◯◯◯ Very low

2 Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ○ Moderate
- ◉ Large

- ○ Varies
- ○ Don't know

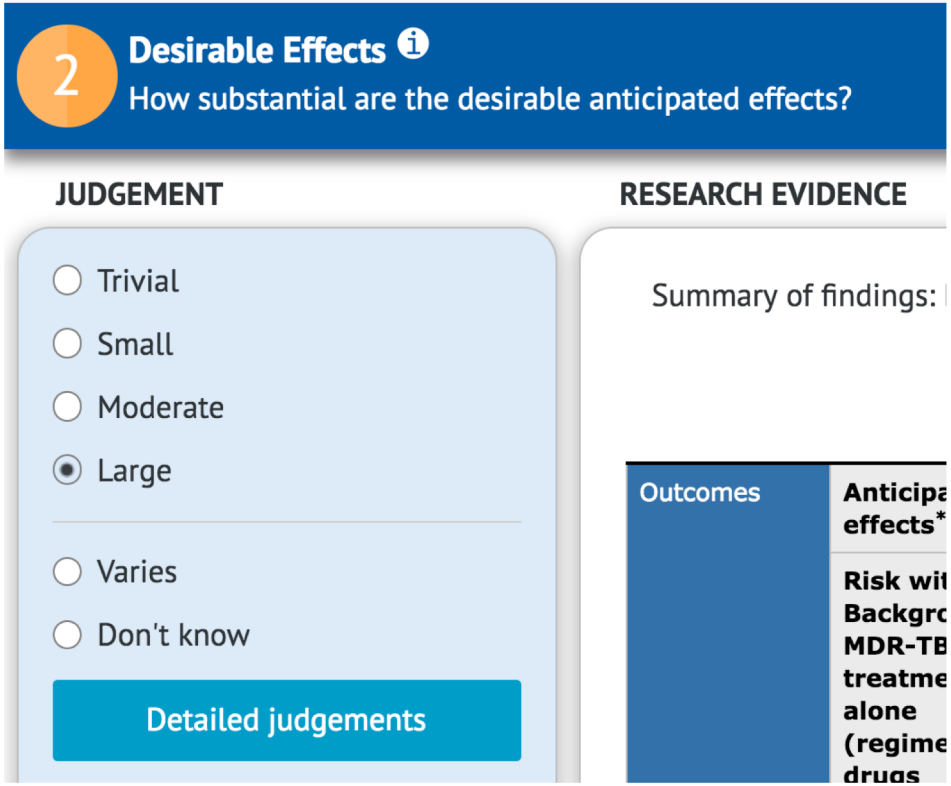
Detailed judgements

RESEARCH EVIDENCE

Summary of findings: Bedaquiline for multidrug-resistant tuberculosis

Collapse table | Open table in new window

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	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) [a,b]	Study population		**RR 1.81** (1.26 to 2.31) [c,d]	132 (1 RCT) [a,c]	⨁⨁◯◯ LOW [e,f]	
	32 per 100 [a]	**58 per 100** (40 to 74) [a]				
Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and	Study population		**RR 3.60** (0.77 to 14.00)	207 (2 RCTs) [g,h]	⨁◯◯◯ VERY LOW [e,i]	
	2 per 100	**7 per 100** (1 to 27) [g]				


2
Desirable Effects
How substantial are the desirable anticipated effects?
JUDGEMENT
RESEARCH EVIDENCE
Trivial
Small
Moderate
Large
Varies
Don't know
Detailed judgements
Summary of findings:
Outcomes
Anticipa
effects*
Risk wit
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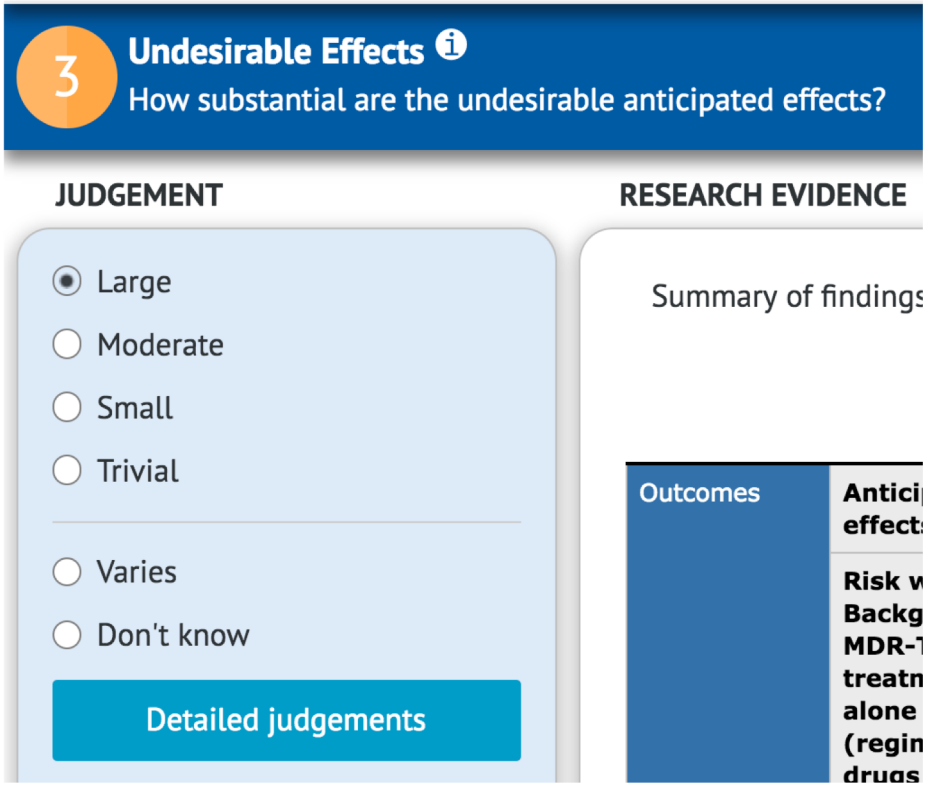
MDR-TB
treatme
alone
(regime
drugs


3
Undesirable Effects
How substantial are the undesirable anticipated effects?
JUDGEMENT
RESEARCH EVIDENCE
Large
Moderate
Small
Trivial
Varies
Don't know
Detailed judgements
Summary of findings
Outcomes
Antici
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drugs

2 Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

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

Detailed judgements

RESEARCH EVIDENCE

Summary of findings:

Outcomes	Anticipa effects*
	Risk wit Backgrc MDR-TB treatme alone (regime drugs

3 Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

Detailed judgements

RESEARCH EVIDENCE

Summary of findings

Outcomes	Antici effect
	Risk w Backg MDR-T treatn alone (regin drugs

4 Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- ◉ Very low
- ○ Low
- ○ Moderate
- ○ High
- ○ No included studies

Detailed judgements

RESEARCH EVIDENCE

ADDITIONAL CONSIDERATIONS

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).

5 Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT

- (•) Important uncertainty or variability
- ( ) Possibly important uncertainty or variability
- ( ) Probably no important uncertainty or variability
- ( ) No important uncertainty or variability

- ( ) No known undesirable outcomes

Detailed judgements

RESEARCH EVIDENCE

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. 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 (panels' opinion). 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 desirable effects probably outweigh the undesirable effects (panels' opinion).

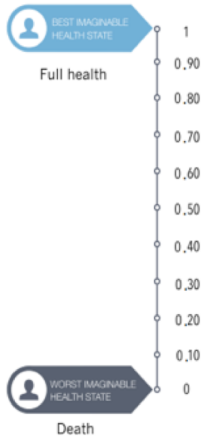
Treatment success (cured by the end of the study), serious adverse events, and mortality were considered critical outcomes to patients, while time to culture conversion and resistance were considered important, but not critical. It is the panels' view that although there is little variability in how 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.

Applying GRADE domains to utility/importance of outcomes

Summary of finding table

Question: What are the views about the relative value/importance of outcomes of interest in decision making for patients with chronic obstructive pulmonary disease?



*Utilities represent the value individuals place on different outcomes. They are measured on an interval scale, with zero reflecting states of health equivalent to death/worst imaginable health and one (or 100 in some cases) reflecting perfect health/ best imaginable health.

Health state/Outcome (Categories of values and preferences)	**Estimates of outcome importance** (range across studies / pooled mean, 95% CI)	**No. of participants /studies**	**Certainty of evidence**	**Interpretation of findings**
Exacerbation (Utility* measured with visual analogue scale [1])	range across studies: 0.259-0.466/ pooled mean: 0.377 (95% CI: 0.294, 0.461) [2]	1076 participants/ 4 studies [2]	⊕⊕⊕◯ Moderate certainty due to inconsistency [2]	Most people find exacerbation of COPD probably has a large impact on lives. There is likely no important variability for this assessment.
Hospitalization (Utility measured with visual analogue scale) [3]	range across studies: 0.259-0.551/ pooled mean: 0.363 (95% CI: 0.161, 0.565) [8]	356 participants/ 3 studies	⊕⊕⊕◯ Moderate certainty due to inconsistency [4]	Most COPD patients find hospitalization probably has a large impact on lives. There is likely no important variability for this assessment.
Intubated (utility measured with visual analogue scale) [5]	Mean (SD): 57.2 (18.2), Median (IQR): 55 (45, 70)	171 participants/ 1 study	⊕⊕⊕◯ Moderate certainty due to risk of bias [5]	Most people find intubation probably has a moderate impact on lives. There is likely no important variability for this assessment.
mechanical ventilation (forced choice) [6]	The proportion of willing to accept the mechanical ventilation ranges from 26% to 77%. Two studies on decision aid suggested decision aid reduced decision conflict or uncertainty.	3470 participants/ 12 studies	⊕◯◯◯ Very low ow certainty due to risk of bias [6] and very serious inconsistency [7]	People seem to prefer to accept mechanical ventilation. There is likely important variability for this assessment.

Balance of the health effects

6 **Balance of effects**

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

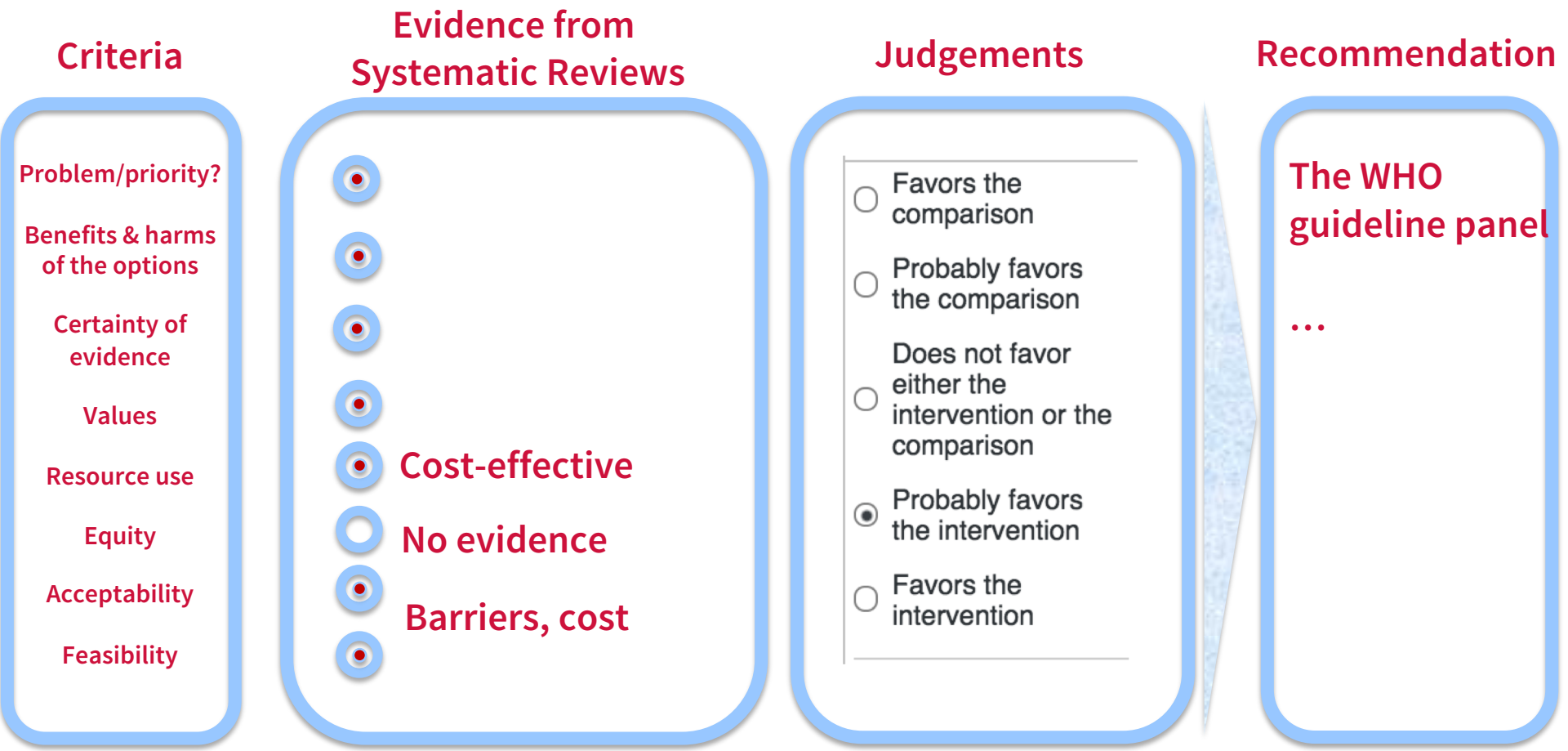
- ○ Favors the comparison
- ○ Probably favors the comparison
- ○ Does not favor either the intervention or the comparison
- ◉ Probably favors the intervention
- ○ Favors the intervention

- ○ Varies
- ○ Don't know

Detailed judgements

RESEARCH EVIDENCE

See evidence profile above


Criteria
Problem/priority?
Benefits & harms of the options
Certainty of evidence
Values
Resource use
Equity
Acceptability
Feasibility
Evidence from Systematic Reviews
Cost-effective
No evidence
Barriers, cost
Judgements
Favors the comparison
Probably favors the comparison
Does not favor either the intervention or the comparison
Probably favors the intervention
Favors the intervention
Recommendation
The WHO guideline panel
…

Criteria

- Problem/priority?
- Benefits & harms of the options
- Certainty of evidence
- Values
- Resource use
- Equity
- Acceptability
- Feasibility

Evidence from Systematic Reviews

- Cost-effective
- No evidence
- Barriers, cost

Judgements

Recommendation

The WHO guideline panel

…

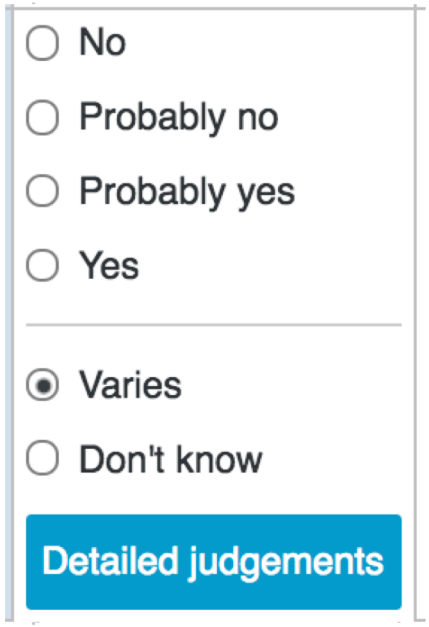
Criteria

- Problem/priority?
- Benefits & harms of the options
- Certainty of evidence
- Values
- Resource use
- Equity
- Acceptability
- Feasibility

Evidence from Systematic Reviews

- Cost-effective
- No evidence
- Barriers, cost

Judgements



Recommendation

The WHO guideline panel

…

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

Bottom panel | Explanations

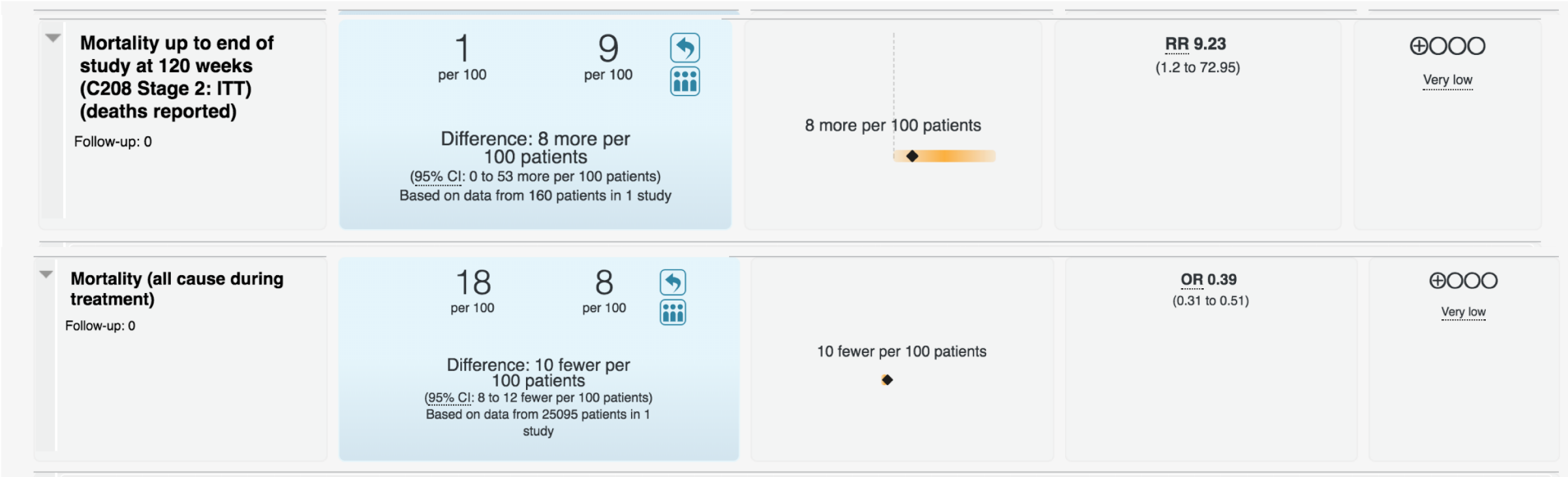
CRITERIA	SUMMARY OF JUDGEMENTS							IMPORTANCE FOR DECISION
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	**HIGH**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	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 comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
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	

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 cohorts, where the following measures are in place. The WHO recommendation for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB is subject to the following five conditions being met:

Mortality 3 years later IPDMA of non-randomized studies



But recommendation unchanged because certainty not higher

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 with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent methodological guideline process on the basis of the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to develop evidence-based guidelines. Our development of specific recommendations for treatment and chemoprophylaxis of sporadic H5N1 infection resulted from the benefits, harms, burden, and cost of interventions in several patient and exposure groups. Overall, the quality of the underlying evidence for all recommendations was rated as very low because it was based on small case series of H5N1 patients, on extrapolation from preclinical studies, and high quality studies of seasonal influenza. A strong recommendation to treat H5N1 patients with oseltamivir was made in part because of the severity of the disease. Similarly, strong recommendations were made to use neuraminidase inhibitors as chemoprophylaxis in high-risk exposure populations. Emergence of other novel influenza A viral subtypes with pandemic potential, or changes in the pathogenicity of H5N1 virus strains, will require an update of these guidelines and WHO will be monitoring this closely.

Lancet Infect Dis 2007; 7: 21–31

Italian National Cancer Institute Regina Elena, INFORMA Unit, Department of Epidemiology, Istituto Regina Elena, Rome, Italy (Prof H J Schünemann MD); **Health Technology and Pharmaceuticals, WHO, Geneva, Switzerland** (S R Hill MD, H Zucker MD); **Norwegian Knowledge Centre for the Health Services, Oslo, Norway** (M Kakad MD, G E Vist PhD, A D Oxman MD); **Department of Infection and Travel Medicine, James Cook University Hospital,**

2 Desirable Effects

How substantial are the desirable anticipated effects?

RESEARCH EVIDENCE

Collapse table | Open table in new window

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Oseltamivir				
Mortality	Study population		not estimable	(0 studies)	-	
	0 per 1.000	**0 per 1.000** (0 to 0)				
Hospitalisation (Hospitalisation from influenza - influenza cases only)	Study population		**RR 0.22** (0.02 to 2.16)	(5 RCTs)	⨁◯◯◯ VERY LOW [a,b]	
	0 per 1.000	**0 per 1.000** (0 to 0)				
Duration of hospitalisation	Study population		not estimable	(0 studies)	-	
	0 per 1.000	**0 per 1.000** (0 to 0)				

ADDITIONAL CONSIDERATIONS

Published animal and in vitro studies were also summarized. The summaries of evidence were then peer reviewed and corrections and comments incorporated by the expert panel. Consistent animal data from three studies in mice indicate that high-dose oseltamivir treatment increased survival in this animal model.

No data from controlled clinical trials of H5N1 infection are available. The existing evidence is based on small observational case series of H5N1 patients, results from in vitro and animal model studies of H5N1, or the extrapolation of data from high quality studies conducted to evaluate the treatment and chemoprophylaxis of normal, or “seasonal”, influenza.

ADDITIONAL CONSIDERATIONS

Published animal and in vitro studies were also summarized. The summaries of evidence were then peer reviewed and corrections and comments incorporated by the expert panel. Consistent animal data from three studies in mice indicate that high-dose oseltamivir treatment increased survival in this animal model.

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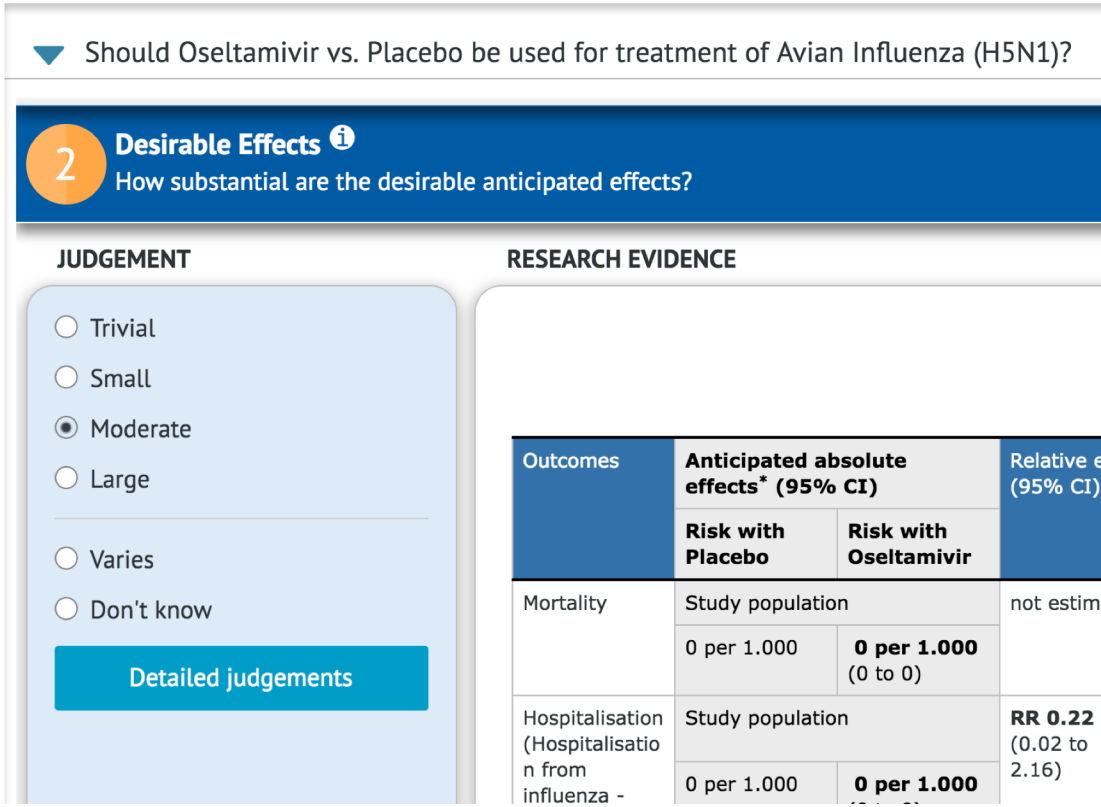
ADDITIONAL CONSIDERATIONS

Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation. Inhaled zanamivir may have lower bioavailability in organ systems other than the respiratory tract (Wong and Yuen 2006).

Judgments are inevitable

Making judgments transparent



EPA/635/R-16/350Fa
www.epa.gov/iris

Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide

(CASRN 75-21-8)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

December 2016

Moberg *et al. Health Research Policy and Systems* (2018) 16:45
https://doi.org/10.1186/s12961-018-0320-2

Health Research Policy and Systems

REVIEW Open Access

The GRADE Evidence to Decision (EtD) framework for health system and public health decisions

Discussion: This framework provides a structured and transparent approach to support policy-making informed by the best available research evidence, while making the basis for decisions accessible to those whom they will affect. The health system and public health EtD framework can also be used to facilitate dissemination of recommendations and enable decision-makers to adopt, and adapt, recommendations or decisions.

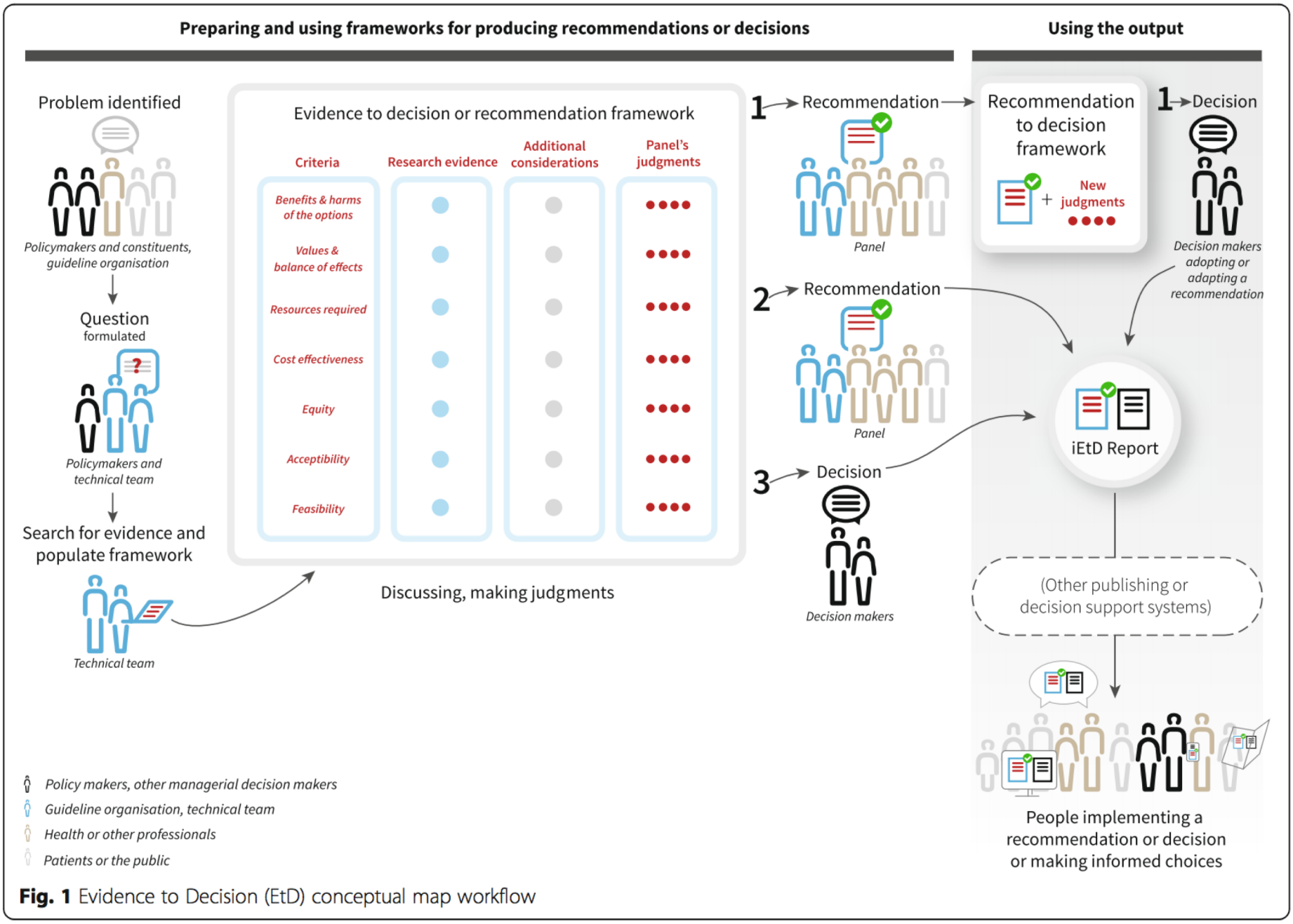
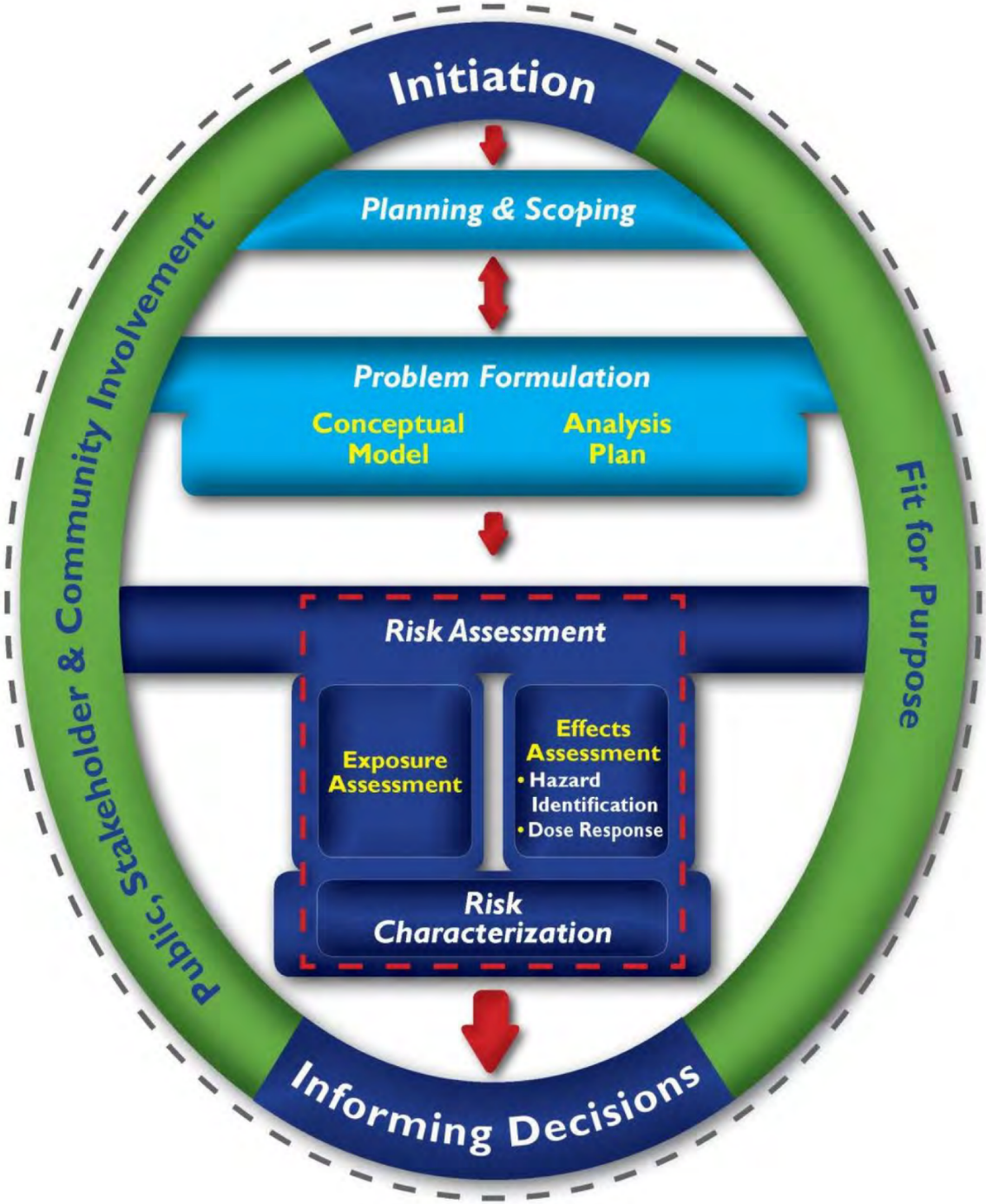


Fig. 1 Evidence to Decision (EtD) conceptual map workflow

EPA/100/R-14/001 April 2014
www.epa.gov/raf

United States
Environmental Protection
Agency

Framework for Human Health Risk Assessment to Inform Decision Making


Initiation
Planning & Scoping
Problem Formulation
Conceptual Model
Analysis Plan
Risk Assessment
Exposure Assessment
Effects Assessment
• Hazard Identification
• Dose Response
Risk Characterization
Informing Decisions
Public, Stakeholder & Community Involvement
Fit for Purpose

EPA 2014

1 Problem

Is the problem a priority?

JUDGEMENT

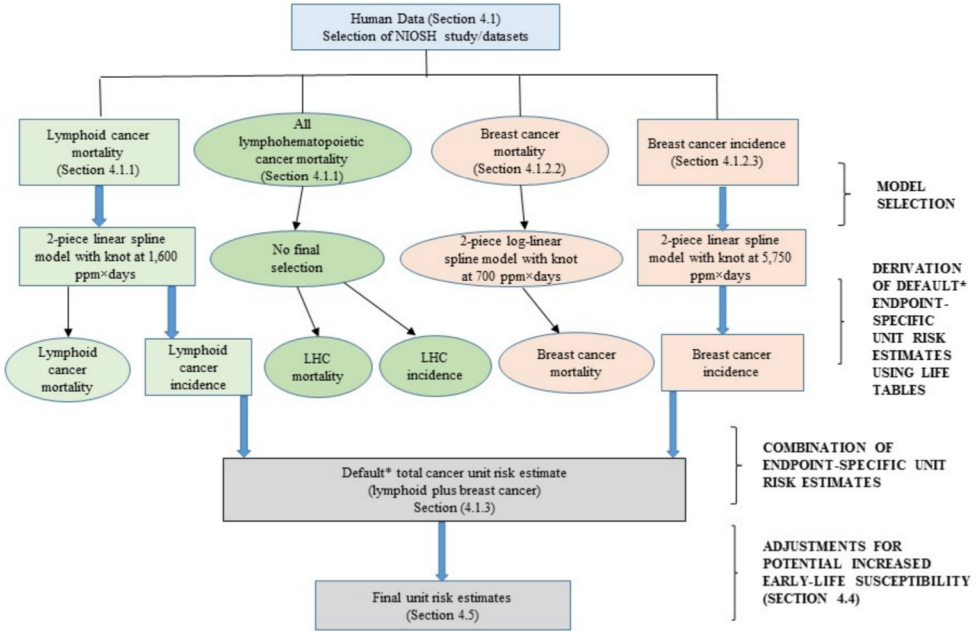
- ○ No
- ○ Probably no
- ○ Probably yes
- ◉ Yes

- ○ Varies
- ○ Don't know

Detailed judgements

RESEARCH EVIDENCE

Ethylene oxide (EtO) is a gas at room temperature. It is manufactured from ethylene and used primarily as a chemical intermediate in the manufacture of ethylene glycol. It is also used as a sterilizing agent for medical equipment and a fumigating agent for spices.
The DNA-damaging properties of EtO have been studied since the 1940s. EtO is known to be mutagenic in a large number of living organisms, ranging from bacteriophage to mammals, and to induce chromosome damage. It is carcinogenic in mice and rats, inducing tumors of the lymphohematopoietic system, brain, lung, connective tissue, uterus, and mammary gland. In humans employed in EtO-manufacturing facilities and in sterilizing facilities, there is strong evidence of an increased risk of cancer of the lymphohematopoietic system and of breast cancer in females. Increases in the risk of lymphohematopoietic cancer have been seen in most (but not all) of the epidemiological studies of EtO-exposed workers, manifested as an increase either in leukemia or in cancer of the lymphoid tissue. Of note, one large epidemiologic study conducted by the National Institute for Occupational Safety and Health (NIOSH) of sterilizer workers that had a well-defined exposure assessment for individuals reported positive exposure-response trends for lymphohematopoietic cancer mortality, primarily in males and in particular for lymphoid cancer (i.e., non-Hodgkin lymphoma [NHL], myeloma, and lymphocytic leukemia), and for breast cancer mortality in females (Steenland et al., 2004).



Should ethylene oxide regulation vs. no regulation be used in sanitation and industry?

Bottom panel | Explanations

2 Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

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

Detailed judgements

RESEARCH EVIDENCE

3.1. EVIDENCE OF CANCER IN HUMANS The literature from 1985, the year of the EPA's previous health assessment document on EtO (U.S. EPA, 1985), to the present contains numerous epidemiological studies of the carcinogenic effects of EtO in occupational cohorts; some of these cohorts were the subject of multiple reports.
3.2. EVIDENCE OF CANCER IN LABORATORY ANIMALS The International Agency for Research on Cancer (IARC) monograph (IARC, 1994b) has summarized the rodent studies of carcinogenicity, and Health Canada (2001) has used this information to derive levels of concern for human exposure.
3.3. SUPPORTING EVIDENCE
3.3.1. Metabolism and Kinetics
3.3.2. Protein Adducts
3.3.3. Genotoxicity

Table 1–1. Summary of major findings

Hazard conclusions	
Hazard characterization	The weight of evidence from epidemiological studies and supporting information is sufficient to conclude that ethylene oxide is carcinogenic to humans.
Mode of action	The weight of evidence is sufficient to conclude that ethylene oxide carcinogenicity has a mutagenic mode of action.
Inhalation unit risk estimates (for environmental exposures)[a]	
Basis	**Inhalation unit risk estimate[a] (per µg/m³)[b]**
Full lifetime unit risk estimate (includes ADAFs)[c]	
Total cancer risk based on human data[d]—lymphoid cancer incidence and breast cancer incidence in females	**5.0×10^{-3}**
Adult-based unit risk estimates (for use with ADAFs)[e]	
Total cancer risk based on human data[d]—lymphoid cancer incidence and breast cancer incidence in females	**3.0×10^{-3}**
Lymphoid cancer incidence in both sexes based on human data	2.6×10^{-3}
Breast cancer incidence in females based on human data	7.0×10^{-4}

ADDITIONAL CONSIDERATIONS

3.4.1. Possible Mechanisms for Mutagenic Mode of Action 3.4.1.1. General Mechanisms Exposure of cells to DNA-reactive agents results in the formation of carcinogen-DNA adducts. The formation of DNA adducts results from a sequence of events involving absorption of the agent, distribution to different tissues, and accessibility of the molecular target (Swenberg et al., 1990).

?

2 Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ○ Trivial
- ○ Small
- ○ Moderate
- ○ Large

- ○ Varies
- ○ Don't know

Detailed judgements

RESEARCH EVIDENCE

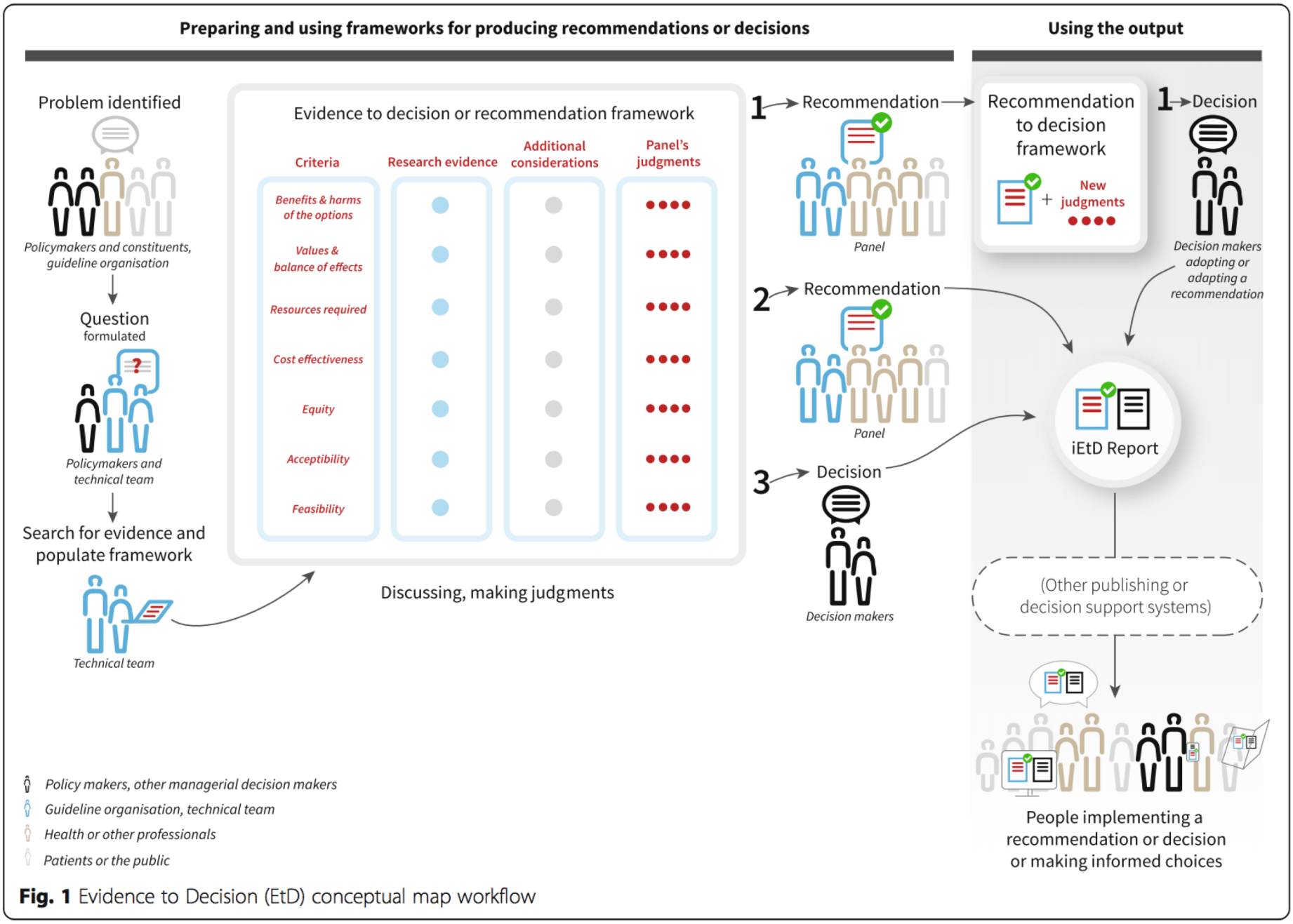


Fig. 1 Evidence to Decision (EtD) conceptual map workflow

Summary

EtDs established process for guideline development

Making Evidence to Decision transparent by separating evidence from opinion

Structured approach that can help policy decision making

Thank you

GRADE in Emergencies & Urgencies

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Preface

Using GRADE to respond to health questions with different levels of urgency

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ABSTRACT

Increasing interest exists in applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to environmental health evidence. While ideally applied to evidence synthesized in systematic reviews and corresponding summary tables, such as evidence profiles, GRADE's correct application requires that "the evidence that was assessed and the methods that were used to identify and appraise that evidence should be clearly described." In this article, we suggest that GRADE could be applied to evidence assembled from narrative reviews, modelled (indirect) evidence, or evidence assembled as part of a rapid response, if the

EFSA´S PROVISIONAL STATEMENT ON A REQUEST FROM THE EUROPEAN COMMISSION RELATED TO MELAMINE AND STRUCTURALLY RELATED COMPOUNDS SUCH AS CYANURIC ACID IN PROTEIN-RICH INGREDIENTS USED FOR FEED AND FOOD

Question N° EFSA-Q-2007-093

BACKGROUND AS SENT BY THE EUROPEAN COMMISSION ON MAY 8TH 2007

Following reports of sickness and death of pet animals (cats and dogs) in the United States (US), an investigation was undertaken by the US authorities to trace the source of these animal health problems. It was found that wheat gluten used for the production of pet food was at the origin of the animal health problems. Recall of pet food in which the wheat gluten was used was initiated in the US from mid-March onwards.

GRADE in urgencies

Organizations in environmental health and other areas looking for structured frameworks for evidence synthesis

- "Fit for purpose" – sometimes systematic review not possible to assemble evidence, i.e., need for emergency response
- GRADE's certainty in the evidence

Table 1
Examples of GRADE applied across different time scenarios.

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Example	West Virginia Elk River spill Population: community exposed to the chemical spill. Intervention/exposure: chemicals in the spill that contaminated water supply. Comparison: no chemicals in the spill. Outcomes: genotoxicity, developmental or reproductive toxicity, liver toxicity and others.	Melamine in composite food products Population: healthy people Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day. Comparison: higher than 0.5 mg/kg body weight of melamine from composition food. Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).	Avian influenza Population: people with suspected avian influenza infection. Intervention/exposure: oseltamivir. Comparison: no oseltamivir. Outcomes: mortality, duration of hospitalization, incidence of lower respiratory tract complications (used for certainty antiviral before tr adverse e	PFOA and birth weight Population: women of reproductive age and fetuses (before and/or during pregnancy or development). Intervention/exposure: perfluorooctanoic acid (PFOA; CAS# 335-67-1) or its salts. Comparison: lower levels of PFOA. l or
Type of evidence	Available evidence: animal toxicology studies in rodents for two chemicals in the spill (a 28-day study and a teratology study) and SAR analyses for other chemicals in the spill with no toxicology data.	Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.	Available trials in p (summar reviews), with avia *in vivo* ar	tic ere
GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judg				*he*
original scenarios).				
Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it	Not serio	n of dies hors rtainty by igh to

Rest of table summarizes:

- GRADE domains
  - risk of bias, imprecision, indirectness, inconsistency, publication bias, magnitude, etc.
- Certainty in evidence
- Possible summary statements

CONCLUSIONS

The Scientific Committee of Food (SCF) derived a tolerable daily intake (TDI) of 0.5 mg/kg body weight (b.w.) per day for melamine for food contact materials but no details were given for its derivation. Recently the U.S. Food and Drug Administration (FDA) derived a TDI of 0.63 mg/kg b.w. per day which is in line with the TDI derived by the SCF. For melamine a specific migration limit of 30 mg/kg food was agreed by the SCF assuming a maximum consumption of 1 kg food containing the substance for a 60 kg person.

Based on the NOAEL for sodium cyanurate derived from the 2-year study in rats of 154 mg/kg b.w. per day, a TDI of 1.5 mg/kg b.w. per day can be proposed using an uncertainty factor of 100.

There is a lack of toxicity data for ammeline and ammelide. Because of the structural similarities to melamine these compounds have been assumed to be of equal potency.

In conclusion, EFSA provisionally recommends to apply a TDI of 0.5 mg/kg b.w. per day for the total of melamine and its analogues (ammeline, ammelide, cyanuric acid). Because of a lack of toxicity data in domestic animals, EFSA provisionally recommends to apply this tolerable intake level as established for humans also to domestic animals.

A source of uncertainty is the combined toxicity of melamine and cyanuric acid and their possible synergistic effects in relation to the recently observed toxicity linked to the acute renal failure and death of pet animals (cats and dogs) in the U.S. This mechanism is currently under investigation.

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Urgent response: one to two weeks

Melamine in composite food products
Population: healthy people
Intervention/exposure: melamine from composition food products below 0.5 mg/kg body weight per day.
Comparison: higher than 0.5 mg/kg body weight of melamine from composition food.
Outcomes: renal insufficiency (assessed with renal clearance), urinary tract calculi, urinary tumors (used for this example of the certainty in the evidence).
Available evidence: animal toxicology studies in rat and mice with exposures to various levels of melamine via feeding, including a control group. The utilized evidence should be supported by a literature search with transparent inclusion and exclusion criteria and a (narrative) summary of that evidence.

GRADE domains to assess certainty in the evidence: suggested approaches to making judgments or proposed judgments (note these are not necessarily reflecting judgments in the original scenarios).

Risk of bias	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, blinding at outcome assessment, sufficient characterization of test compound, or whether all animals were accounted for). Ideally, RoB assessments would be available for individual studies and summarized across studies. In the Elk River example, the number of animal studies was small and could be assessed at the individual level within a short-time frame. A de novo risk of bias evaluation may not be feasible in cases where evidence is drawn from existing narrative risk assessments that summarize a large body of literature. Nevertheless, it may still be possible to assess risk of bias based on the uncertainties and evidence limitations described in the risk assessment. SAR: could be assessed using OECD model validation or similar guidance that recommends presentation of a defined domain of applicability for a defined endpoint supported by appropriate measures of goodness-of-fit (OECD, 2007).	Animal studies: would be assessed by risk of bias (RoB) considerations for animal studies (e.g. randomization, pathologists blinded in their assessments or all animals accounted for). In this case it appears that the animal studies did not report that it was randomized and, thus, may be at risk of bias.	Not serious	Serious based on some concern of risk of bias in the included studies (in the original report, the authors used an approach to rating certainty that accounted for risk of bias by lowering the certainty from high to moderate).
Imprecision	Could be assessed for both animal data and SAR (e.g., considering statistical or numerical uncertainty in model parameters).	While no summary estimates are available, an assessment could be guided by the availability of data from only 100 animals in different exposure groups which would result in wide confidence intervals.	Serious	Not serious
Inconsistency	Could be assessed for both animal data and SAR (e.g., assessing similarity of results based on applying different models).	Only one study was included and therefore no inconsistency is present (Guyatt et al., 2011d).	Not serious	Not serious

Type of response	Ultra-short emergency response: within one or more hours	Urgent response: one to two weeks	Rapid response: one to three months	Routine response: more than 3 months
Indirectness	Animal studies: could be assessed using GRADE's indirectness assessment (Guyatt et al., 2011c; Schünemann et al., 2013). Animal studies may be rated down for indirectness if concerns exist about extrapolating from animals to humans, e.g., relevance of animal model for the health outcome of interest or route of exposure. SAR: could be assessed based on evidence of direct relation of the model to a defined endpoint. SAR would typically be downgraded for indirectness.	This could be rated down for serious indirectness of extrapolating from animals to humans and uncertainty about the levels of exposure (different levels or routes of exposure evaluated than those one is interested in and modeling of exposure levels based on composition food products from more exact exposures fed to animals). Further concerns would likely be described for the comparator.	Very serious	Not serious
Possible summary statement*	There is low certainty in the evidence suggesting no association between the exposure and toxicity based on SAR analyses.	There is very low certainty in the evidence suggesting no association between levels of melamine exposure from composition food products below 0.5 mg/kg body weight per day and urinary tumors.	There is very low certainty suggesting that oseltamivir reduces hospitalization in patients with avian influenza.	There is moderate certainty in the evidence suggesting that PFOA is associated with harmful effects on fetal growth.

* Note, this hypothetical summary was derived by the authors of this editorial, not those of the original report.