GRADEpro: eine web-basierte Lösung für die Zusammenfassung, Darstellung und Vermittlung von Wissen für klinische Entscheidungen
“Birthplace of evidence-based medicine and problem based learning”

Disclosures

- Director
- Co-chair

Cochrane Canada
GRADE working group
GIN Board, Member

Views expressed are my own
Content
GRADE in the context of guideline development
GRADEpro Guideline Development Tool
• Examples of application
  • World Health Organization Guidelines
  • European Commission Initiative on Breast Cancer and ARIA allergic rhinitis guidelines
  • American Society of Hematology
• GRADEpro Panelvoice
• GRADE-based interactive Decision Aids
Guideline development Process

American Thoracic Society Documents

A Guide to Guidelines for Professional Societies and Other Developers of Recommendations
Introduction to Integrating and Coordinating Efforts in COPD Guideline Development. An Official ATS/ERS Workshop Report

Holger J. Schünemann, Mark Woodhead, Antonio Anzueto, A. Sonia Buist, William MacNee, Klaus F. Rabe, and John Heffner; on behalf of the ATS/ERS Ad Hoc Committee on Integrating and Coordinating Efforts in COPD Guideline Development


Health Research Policy and Systems

Review

Improving the use of research evidence in guideline development: introduction
Andrew D Oxman¹, Atle Fretheim¹, Holger J Schünemann² and SURE³

Published: 21 November 2006
Received: 07 April 2006
Accepted: 21 November 2006


This article is available from: http://www.health-policy-systems.com/content/4/1/13
Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise

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

Abstract

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

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

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

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

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

This article has been peer reviewed.

Correspondence to: Holger Schünemann, schuneh@mcmaster.ca

**Tool of 18 topics with resources 144 items**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Organization, budget, planning and training</td>
<td>Involves laying out a general but detailed plan describing what is feasible, how it will be achieved and what resources are required to produce and use the guideline. The plan should refer to a specific period and be expressed in formal, measurable terms.</td>
</tr>
<tr>
<td>2. Priority setting</td>
<td>Refers to the identification, balancing and ranking of priorities by stakeholders. Priority setting ensures that resources and attention are devoted to those general areas (e.g., chronic obstructive pulmonary disease, diabetes, cardiovascular disease, cancer, prevention) where health care recommendations will provide the greatest benefit to the population, a jurisdiction or a country. A priority-setting approach needs to contribute to future plans while responding to existing, potentially difficult circumstances.</td>
</tr>
<tr>
<td>3. Guideline group membership</td>
<td>Defines who is involved, in what capacity, and how the members are selected for the guideline development and at other steps of the guideline enterprise.</td>
</tr>
<tr>
<td>4. Establishing guideline group processes</td>
<td>Defines the steps to be followed, how those involved will interact and how decisions will be made.</td>
</tr>
<tr>
<td>5. Identifying target audience and topic selection</td>
<td>Involves describing the potential users or consumers of the guideline and defining the topics to be covered in the guideline (e.g., diagnosis of chronic obstructive pulmonary disease).</td>
</tr>
<tr>
<td>6. Consumer and stakeholder involvement</td>
<td>Describes how relevant people or groups who are not necessarily members of the panel but are affected by the guideline (e.g., as target audience or users) will be engaged.</td>
</tr>
<tr>
<td>7. Conflict of interest considerations</td>
<td>Focuses on defining and managing the potential divergence between an individual’s interests and his or her professional obligations that could lead to questioning whether the actions or decisions are motivated by gain, such as financial, academic advancement, clinical revenue streams or community standing. Financial or intellectual or other relationships that may affect an individual’s or organization’s ability to approach a scientific question with an open mind are included.</td>
</tr>
<tr>
<td>8. Question generation</td>
<td>Focuses on defining key questions the recommendations should address using the PICO (patient/problem, intervention, comparison, outcome) framework, including the detailed population, intervention (including diagnostic tests and strategies) and outcomes that will be relevant for decision-making (e.g., should test A be used, or should treatments B, C, D or E be used in chronic obstructive pulmonary disease?).</td>
</tr>
</tbody>
</table>
9. Considering importance of outcomes and interventions, values, preferences and utilities

Includes integrating, in the process of developing the guidelines, how those affected by its recommendations assess the possible consequences. These include patient, caregiver and health care provider knowledge, attitudes, expectations, moral and ethical values, and beliefs; patient goals for life and health; prior experience with the intervention and the condition; symptom experience (e.g., breathlessness, pain, dyspnea, weight loss); preferences for and importance of desirable and undesirable outcomes; perceived impact of the condition or interventions on quality of life, well-being or satisfaction, and interactions between the work of implementing the intervention, the intervention itself, and other contexts the patient may be experiencing; preferences for alternative courses of action; and preferences relating to communication content and styles, information and involvement in decision-making and care. This can be related to what in the economic literature is considered *utilities*. An intervention itself can be considered a consequence of a recommendation (e.g., the burden of taking a medication or undergoing surgery) and a level of importance or value is associated with that.

10. Deciding what evidence to include and searching for evidence

Focuses on laying out inclusion and exclusion criteria based on types of evidence (e.g., rigorous research, informally collected), study designs, characteristics of the population, interventions and comparators, and deciding how the evidence will be identified and obtained. It also includes but is not limited to evidence about values and preferences, local data and resources.

11. Summarizing evidence and considering additional information

Focuses on presenting evidence in a synthetic format (e.g., tables or brief narratives) to facilitate the development and understanding of recommendations. It also involves identifying and considering additional information relevant to the question under consideration.

12. Judging quality, strength or certainty of a body of evidence

Includes assessing the confidence one can place in the obtained evidence by transparently evaluating the obtained research (individual studies and across studies) and other evidence applying structured approaches. This may include, but is not limited to, evidence about baseline risk or burden of disease, importance of outcomes and interventions, values, preferences and utilities, resource use (cost), estimates of effects and accuracy of diagnostic tests.

13. Developing recommendations and determining their strength

Developing recommendations involves use of a structured analytic framework and a transparent and systematic process to integrate the factors that influence a recommendation. Determining the strength of the recommendations refers to judgments about how confident a guideline panel is that the implementation of a recommendation exerts more desirable than undesirable consequences.

14. Wording of recommendations and of considerations about implementation, feasibility and equity

Refers to choosing syntax and formulations that facilitate understanding and implementation of the recommendations. Such wording is connected to considerations about implementation, feasibility and equity, which refer to the guideline panel’s considerations about how the recommendation will be used and what impact it may have on the factors described.

15. Reporting and peer review

Reporting refers to how a guideline will be made public (e.g., print, online). Peer review refers to how the guideline document will be reviewed before its publication and how it can be assessed (e.g., for errors), both internally and externally, by stakeholders who were not members of the guideline development group.

16. Dissemination and implementation

Focuses on strategies to make relevant groups aware of the guidelines and to enhance their uptake (e.g., publications and tools such as mobile applications).

17. Evaluation and use

Refers to formal and informal strategies that allow judgments about: evaluation of the guidelines as a process and product; evaluation of the use or uptake, or both; and evaluation of impact and whether or not the guideline leads to improvement in patient or population health or other consequences.

18. Updating

Refers to how and when a guideline requires revision because of changes in the evidence or other factors that influence the recommendations.
Interactive website
ccebgrade.mcmaster.ca/guidecheck.html

GIN-McMaster Guideline Development Checklist

About the Checklist

This is a webpage for the GIN-McMaster Guideline Development Checklist, which contains a comprehensive list of topics and items outlining the practical steps to consider for developing guidelines. The Guideline Development Checklist project is a partnership between the Guidelines International Network (GIN) and McMaster University. The checklist is intended for use by guideline developers to plan and track the process of guideline development and to help ensure that no key steps are missed. Users of the checklist should become familiar with the topics and the items before applying them.

What the Checklist is and what it isn't:

The checklist is designed to serve as a publicly available and interactive resource, with links to learning tools and training materials, for those interested in beginning, enhancing or evaluating their guideline development process. Considering items on this checklist is intended to support the development and implementation of trustworthy guidelines.

The purpose of the checklist is not to replace guideline credibility assessment tools like AGREE and other tools that may be a result of standards put forth by the Guidelines International Network or Institute of Medicine (IOM). Following steps outlined in the checklist will, however, ensure that key items are covered and increase the likelihood of the guideline achieving higher scores when evaluated with credibility assessment tools.

See our publication in the Canadian Medical Association Journal for a detailed explanation of the guideline checklist and its development.
Please also view the two videos below to learn about the features of each version of the checklist.

The Guideline Development Checklist is officially endorsed by:

Developed in collaboration with:
Priority Setting
Updating
Conflict-of-Interest Considerations
Guideline Group Membership & Processes
Documenting Guideline Development Process & Decisions

Organization, Budget, Planning & Training

Oversight Committee
Guideline Group Membership & Processes
Guideline Panel
Working Groups

Target Audience & Topic Selection
(PICO) Question Generation
Summarizing Evidence & Considering Additional Information
Judging Quality, Strength or Certainty of Body of Evidence

Developing Recommendations & Determining their Strength
Wording of Recommendations
Reporting & Peer Review
Dissemination & Implementation
Evaluation & Use
Updating

Effects (Interventions, Diagnostic Tests)
Importance of Outcomes and Interventions, Values, Preferences & Utilities
Baseline Risk, Burden of Disease, Resource Use, Effects on Equity & Other Information

http://cebgrade.mcmaster.ca/guidecheck.html
After 30 years of increasing confusion, GRADE developed a unifying, transparent and sensible system for grading the certainty of evidence and making decisions

- Over 100 organizations: WHO, European Commission, NICE, CADTH, CDC, professional societies, academics
- For systematic reviews, HTA and guidelines
- International & diverse contributors (>600)
- 2008 BMJ series; 2011 JCE series – over 30,000 cites
- Various other publications (incl. GRADE Handbook)
- Official IT applications GRADEpro GDT
**Evidence synthesis (systematic review/HTA)**

- **P (Problem)**: Outcomes
  - Critical
  - Important
  - Not important

- **I/E (Intervention/Effect)**: Outcomes
  - Critical

- **C (Comparison)**: Outcomes
  - Important

- **O (Outcome)**: Create evidence profile or summary of findings
  - Table with GRADEpro

**Randomization raises initial quality**
- Grade down
  - 1. Risk of bias
  - 2. Inconsistency
  - 3. Indirectness
  - 4. Imprecision
  - 5. Publication bias

**Grade up**
- 1. Large effect
- 2. Dose response
- 3. Opposing bias & Confounders

**Certainty of evidence for each outcome**
- High
- Moderate
- Low
- Very low

**Grade overall Certainty of evidence across outcomes**

**Recommendation/Decision**

- Grade recommendations (Evidence to Recommendation)
  - For or against (direction) \( \downarrow \uparrow \)
  - Strong or conditional/weak (strength)

- By balancing consequences (evidence to recommendations):
  - Certainty of evidence
  - Values and preferences (utilities)
  - Balance benefits/harms
  - Resource use (cost)
  - Equity, Feasibility, Acceptability

**Formulate Recommendations** (\( \downarrow \uparrow | \oplus ... \))
- “The panel recommends that ….should...”
- “The panel suggests that ….should...”
- “The panel suggests to not ...”
- “The panel recommends to not...”

**EtD framework**
GRADE decision criteria

Systematic reviews or HTA

- Problem size and priority
- Benefits & harms of the options
  - Values
  - Resource use
  - Equity
  - Acceptability
  - Feasibility
- Evidence where available

Recommendation
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 Oxman4 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

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 , Marjo Holtman k , Patrick Reuten g , Andrew D. Oxman l , GRADE Working Group
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-Coello1,10 and Holger J. Schünemann1,6*

Transparent Development of the WHO Rapid Advice Guidelines

Key Problems

1. Time is short
2. Money is tight
3. Guidelines are complicated (and shouldn’t be simplistic)
GRADE's software for Summary of Findings tables, Health Technology Assessment and Guidelines
WHO Guideline on the use of Bedaquiline for Drug Resistant Tuberculosis

GRADEpro Evidence to Decision Frameworks piloting
Grading of evidence
Updating of guidelines
The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interim policy guidance


A review of available evidence (2016)

28 - 29 June 2016
Geneva, Switzerland

World Health Organization

THE END TB STRATEGY
<table>
<thead>
<tr>
<th>Project Description</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ATS] IPF: Management (21 questions)</td>
<td>ATS</td>
</tr>
<tr>
<td>[CPG] GLAD-P (PRE and PRObiotics)</td>
<td></td>
</tr>
<tr>
<td>[CPG] GLAD-P (PRE and PRObiotics) Holger working copy</td>
<td></td>
</tr>
<tr>
<td>[CPG] GLAD-P Vitamin D</td>
<td></td>
</tr>
<tr>
<td>[WAO] GLAD-P: PRE and PRObiotics</td>
<td>WAO</td>
</tr>
<tr>
<td>2016 Update of WHO Interim guidelines on the use of Delamanid in MDR TB</td>
<td></td>
</tr>
<tr>
<td>2016 Update of WHO Interim guidelines on the use of Delamanid in MDR TB working copy</td>
<td></td>
</tr>
<tr>
<td>2nd Example heparin for patients with cancer who have no other indication for heparin</td>
<td></td>
</tr>
<tr>
<td>Adaptation of Rheumatoid Arthritis Guidelines for the Eastern Mediterranean Region</td>
<td></td>
</tr>
<tr>
<td>ARIA 2015 [original]</td>
<td>ARIA</td>
</tr>
<tr>
<td>ASH Guideline on Diagnosis of VTE</td>
<td>ASH</td>
</tr>
<tr>
<td>ASH Guideline on Diagnosis of VTE</td>
<td>ASH</td>
</tr>
<tr>
<td>ASH Guideline on Heparin-Induced Thrombocytopenia (HIT)</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Optimal Management of Anticoagulation Therapy</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Pediatric VTE (Working Copy)</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Prevention and Treatment of VTE in Patients with Cancer</td>
<td></td>
</tr>
</tbody>
</table>

- **Language Options:**
  - English
  - 中国 (Chinese)
  - Deutsch
  - Español
  - Italiano
  - 日本語 (Japanese)
  - Nederlands
  - Português
  - Eesti
<table>
<thead>
<tr>
<th>Project Description</th>
<th>Legacy</th>
<th>Active</th>
<th>Archived</th>
<th>Invitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ATS] IPF: Management (21 questions)</td>
<td>--</td>
<td>Aug 2, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>[CPG] GLAD-P (PRE and PRObiotics)</td>
<td>--</td>
<td>Nov 14, 2016 by me</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>[CPG] GLAD-P (PRE and PRObiotics) Holger working copy</td>
<td>--</td>
<td>Jun 26, 2016 by me</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>[CPG] GLAD-P Vitamin D</td>
<td>--</td>
<td>Nov 22, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>[WAO] GLAD-P: PRE and PRObiotics</td>
<td>WAO</td>
<td>Jun 12, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>2016 Update of WHO Interim guidelines on the use of Delamanid in MDR TB</td>
<td>--</td>
<td>Nov 17, 2017 by me</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>2016 Update of WHO Interim guidelines on the use of Delamanid in MDR TB working copy for WHO report</td>
<td>--</td>
<td>May 16, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>2nd Example heparin for patients with cancer who have no other indication for heparin</td>
<td>--</td>
<td>Nov 24, 2017 by me</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Adaptation of Rheumatoid Arthritis Guidelines for the Eastern Mediterranean Region</td>
<td>--</td>
<td>Nov 18, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ARIA 2015 [original]</td>
<td>ARIA</td>
<td>Jul 31, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Diagnosis of VTE</td>
<td>ASH</td>
<td>Nov 17, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Diagnosis of VTE</td>
<td>ASH</td>
<td>Nov 6, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Heparin-Induced Thrombocytopenia (HIT)</td>
<td>--</td>
<td>Aug 23, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Optimal Management of Anticoagulation Therapy</td>
<td>--</td>
<td>Nov 16, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Pediatric VTE (Working Copy)</td>
<td>--</td>
<td>Jul 28, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Prevention and Treatment of VTE in Patients with Cancer</td>
<td>--</td>
<td>Nov 17, 2017</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Project Description</td>
<td>Status</td>
<td>Date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>----------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ATS] IFF: Management (21 questions)</td>
<td>AFS</td>
<td>Aug 2, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CAP) GLAD-P (PRE and PRObiotics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CAP) GLAD-P (PRE and PRObiotics) Images working copy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CAP) GLAD-P Vitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO) GLAD-P, PRE and PRObiotics</td>
<td>WAQ</td>
<td>Jun 12, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016 Update of WHO interim guidelines on the use of Drotaban in MDR-TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016 Update of WHO interim guidelines on the use of Drotaban in MDR-TB with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Example heparin for patients with cancer who have no other indication for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptation of Rheumatoid Arthritis Guidelines for the Eastern Mediterranean Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIA 2015 (original)</td>
<td>ARIA</td>
<td>Jul 31, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Diagnosis of VTE</td>
<td>ASH</td>
<td>Nov 17, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Diagnosis of VTE</td>
<td>ASH</td>
<td>Nov 6, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Heparin-Induced Thrombocytopenia (HIT)</td>
<td></td>
<td>Aug 23, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Optimal Management of Anticoagulation Therapy</td>
<td></td>
<td>Nov 16, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Pediatric VTE (Working Copy)</td>
<td></td>
<td>Mar 3, 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASH Guideline on Prevention and Treatment of VTE in Patients with Cancer</td>
<td></td>
<td>Nov 17, 2017</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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. Special measures need to be put in place to ensure the early detection and timely reporting of adverse events using active pharmacovigilance methods, such as ‘cohort event monitoring’. Any adverse drug reaction attributed to bedaquiline should also be reported to the national pharmacovigilance centre as part of the spontaneous reporting mechanism in the country. As for any other drug in the MDR-TB regimen the patient should be encouraged to report to the attending health worker any adverse event that occurs during the time the drug is being
GRADE standard EtD templates were developed to facilitate the process of making healthcare decisions by guideline panels. Different EtD templates include various criteria (e.g., equity) depending on type of recommendations/decisions and chosen perspective (e.g., individual, population). Learn about EtD templates

Template for management questions
- Clinical recommendation - Individual perspective
- Clinical recommendation - Population perspective
- Coverage Decision
- Health system and public health recommendation
- Health system and public health decision

> Question

> Assessment

> Conclusions

> Presentations
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?
### 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)?

### Assessment

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the problem a priority?</td>
<td>Yes</td>
<td>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].</td>
</tr>
<tr>
<td>How substantial are the desirable anticipated effects?</td>
<td>Large</td>
<td>Summary of findings: Bedaquiline for multidrug-resistant tuberculosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO) in MDR-TB patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Presentation and use of criteria can be tailored

Interactive EtDs (iEtD)
Lets us choose the criteria
If obvious or not considered omit
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
What are guideline panel members doing?
Discuss evidence

**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)?

**Assessment**

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the problem a priority?</td>
<td>Yes</td>
<td>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].</td>
</tr>
</tbody>
</table>
| How substantial are the desirable anticipated effects? | Large     | Summary of findings: Bedaquiline for multidrug-resistant tuberculosis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with</td>
<td>Risk with</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Add relevant 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) 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).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative importance</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)</td>
<td>CRITICAL</td>
<td>☃️oston LOW</td>
</tr>
<tr>
<td>Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)</td>
<td>CRITICAL</td>
<td>☃️ston VERY LOW</td>
</tr>
<tr>
<td>Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)</td>
<td>CRITICAL</td>
<td>☃️ston VERY LOW</td>
</tr>
<tr>
<td>Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MG1T960)</td>
<td>CRITICAL</td>
<td>☃️ston LOW</td>
</tr>
<tr>
<td>Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with</td>
<td>CRITICAL</td>
<td>☃️ston</td>
</tr>
</tbody>
</table>
Make judgments (when research evidence complete) – w/o COI

<table>
<thead>
<tr>
<th>How substantial are the desirable anticipated effects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ Trivial</td>
</tr>
<tr>
<td>○ Small</td>
</tr>
<tr>
<td>○ Moderate</td>
</tr>
<tr>
<td>○ Varies</td>
</tr>
<tr>
<td>○ Don’t know</td>
</tr>
</tbody>
</table>

**Summary of findings: Bedaquiline for multidrug-resistant tuberculosis**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO)</td>
<td>Risk with Background MDR-TB treatment alone (regimen of drugs recommended by WHO)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects cured by end of study: 120-weeks (C208 Stage 2: mITT)</td>
<td>RR 1.81 (1.26 to 2.33)</td>
<td>132 (1 RCT)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>32 per 100</td>
<td>58 per 100 (40 to 74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Events during Investigational 24 week treatment phase (C208 Stages 1 and 2)</td>
<td>RR 3.60 (0.77 to 14.00)</td>
<td>207 (2 RCTs)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>2 per 100</td>
<td>7 per 100 (1 to 27)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Interactive Summary of Findings

### Tables

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

#### Cured by end of study
- **Follow-up:** 120 weeks  
- **Plain language summary:** Bedaquiline may increase the number of patients cured.  
- **Absolute Effect**
  - **Without bedaquiline:** 32\(\frac{1}{100}\)  
  - **With bedaquiline:** 58\(\frac{1}{100}\)  
  - **Difference:** 26 more per 100 patients

**Relative effect**
- **RR:** 1.81 (1.26 to 2.31)  
- **N\(\circ\) of participants & studies:** Based on data from 132 patients in 1 study

**Certainty of the evidence**
- **GRADE:** Low

#### Serious adverse events
- **Follow-up:** 24 week treatment phase  
- **Plain language summary:** It is uncertain whether bedaquiline increases the number of patients who have adverse effects.  
- **Absolute Effect**
  - **Without bedaquiline:** 2\(\frac{1}{100}\)  
  - **With bedaquiline:** 7\(\frac{1}{100}\)  
  - **Difference:** 5 more per 100 patients

**Relative effect**
- **RR:** 3.6 (0.77 to 14.00)  
- **N\(\circ\) of participants & studies:** Based on data from 207 patients in 2 studies

**Certainty of the evidence**
- **GRADE:** Very low

#### Mortality
- **Follow-up:** 120 weeks  
- **Plain language summary:** It is uncertain whether bedaquiline increases the number of patients who die.  
- **Absolute Effect**
  - **Without bedaquiline:** 3\(\frac{1}{100}\)  
  - **With bedaquiline:** 13\(\frac{1}{100}\)  
  - **Difference:** 10 more per 100 patients

**Relative effect**
- **RR:** 9.23 (1.20 to 72.96)  
- **N\(\circ\) of participants & studies:** Based on data from 160 patients in 1 study

**Certainty of the evidence**
- **GRADE:** Very low
Detailed judgements

**DESIRABLE EFFECTS:** How substantial are the desirable anticipated effects?

**Panel discussion**

---

**Detailed questions**

How substantial is the anticipated effect (difference) for each main outcome for which there is a desirable effect?

<table>
<thead>
<tr>
<th>Main outcomes</th>
<th>Judgements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)</td>
<td>Trivial Small Moderate Large Varies Don't know</td>
</tr>
<tr>
<td>Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)</td>
<td>Trivial Small Moderate Large Varies Don't know</td>
</tr>
<tr>
<td>Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)</td>
<td>Trivial Small Moderate Large Varies Don't know</td>
</tr>
<tr>
<td>Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGit960)</td>
<td>Trivial Small Moderate Large Varies Don't know</td>
</tr>
<tr>
<td>Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGit960)</td>
<td>Trivial Small Moderate Large Varies Don't know</td>
</tr>
</tbody>
</table>
Outcome: Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)

<table>
<thead>
<tr>
<th>Domain (original question asked)</th>
<th>Description</th>
<th>Judgment - Is the evidence sufficiently direct?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population:</td>
<td></td>
<td>Yes  Probably yes  Probably no  No</td>
</tr>
<tr>
<td>Intervention: Bedaquiline + background MDR-TB treatment</td>
<td></td>
<td>Yes  Probably yes  Probably no  No</td>
</tr>
<tr>
<td>Comparator: Background MDR-TB treatment alone (regimen of drugs recommended by WHO)</td>
<td></td>
<td>Yes  Probably yes  Probably no  No</td>
</tr>
<tr>
<td>Direct comparison</td>
<td></td>
<td>Yes  Probably yes  Probably no  No</td>
</tr>
<tr>
<td>Outcome: Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)</td>
<td></td>
<td>Yes  Probably yes  Probably no  No</td>
</tr>
<tr>
<td>Final judgment about indirectness across domains:</td>
<td></td>
<td>No indirectness  Serious indirectness  Very serious indirectness</td>
</tr>
</tbody>
</table>

Cancel  Apply
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.

Results were ambiguous in low-income settings, and highly dependent on the assumptions made about the generalizability of trial results to routine settings. The expert group noted that further analysis would be needed to test the robustness of the assumptions in various settings and to separately assess affordability [1].
<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>SUMMARY OF JUDGEMENTS</th>
<th>FAVORS background...</th>
<th>FAVORS bedaquiline...</th>
<th>IMPORTANCE FOR DECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROBLEM</td>
<td>No</td>
<td>Probably no</td>
<td>Probability yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DESIRABLE EFFECTS</td>
<td>Trivial</td>
<td>Small</td>
<td>Moderate</td>
<td>Large</td>
</tr>
<tr>
<td>UNDESIRABLE EFFECTS</td>
<td>Large</td>
<td>Moderate</td>
<td>Small</td>
<td>Trivial</td>
</tr>
<tr>
<td>CERTAINTY OF EVIDENCE</td>
<td>Very low</td>
<td>Important uncertainty or...</td>
<td>Possibly important...</td>
<td>No important uncertainty...</td>
</tr>
<tr>
<td>VALUES</td>
<td>Important uncertainty or...</td>
<td>Possibly important...</td>
<td>Probably no important...</td>
<td>No important uncertainty...</td>
</tr>
<tr>
<td>BALANCE OF EFFECTS</td>
<td>Favors the comparison</td>
<td>Probably favors the...</td>
<td>Doesn't favor either the...</td>
<td>Probably favors the...</td>
</tr>
<tr>
<td>RESOURCES REQUIRED</td>
<td>Large costs</td>
<td>Moderate costs</td>
<td>Negligible costs and...</td>
<td>Moderate savings</td>
</tr>
<tr>
<td>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>COST EFFECTIVENESS</td>
<td>Favors the comparison</td>
<td>Probably favors the...</td>
<td>Doesn't favor either the...</td>
<td>Probably favors the...</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Reduced</td>
<td>Probably reduced</td>
<td>Probably no impact</td>
<td>Probably increased</td>
</tr>
<tr>
<td>ACCEPTABILITY</td>
<td>No</td>
<td>Probably no</td>
<td>Probability yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>No</td>
<td>Probably no</td>
<td>Probability yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**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?**

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>Strong recommendation against the intervention</th>
<th>Conditional recommendation against the intervention</th>
<th>Conditional recommendation for either the intervention or the comparison</th>
<th>Conditional recommendation for the intervention</th>
<th>Strong recommendation for the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1.png" alt="image" /></td>
<td><img src="image2.png" alt="image" /></td>
<td><img src="image3.png" alt="image" /></td>
<td><img src="image4.png" alt="image" /></td>
<td><img src="image5.png" alt="image" /></td>
</tr>
</tbody>
</table>

**Recommendation**

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

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 prolonging drugs then possible avoid use. E.g. PLHIV. Need to monitor ECG in these patients.
- Do not apply to children - risk are too high.

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

**Subgroup considerations**

Bedaquiline is only suggested for patients with extensively drug-resistant (XDR) tuberculosis and limited, if any other options, the desirable effects probably outweigh the undesirable effects.

**Implementation considerations**

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

**Monitoring and evaluation**

- Spontaneous reporting of adverse drug reactions should be reinforced at country level and active pharmacovigilance should be established among patient groups treated with the drug.
- Resistance to bedaquiline should be monitored.
- Resistance to other anti-TB drugs should be monitored following WHO recommendations.

**Research priorities**

- Phase 3 clinical trial(s) of safety and efficacy of bedaquiline, with particular attention to mortality (including causes of death), in the treatment of MDR-TB should be accelerated.
- Pharmacokinetics, safety and efficacy studies in specific populations (paediatrics, HIV patients, alcohol and drug users, elderly, pregnant women, extrapulmonary TB, persons with diabetes).
- Safety studies, including type, frequency and severity of adverse events (short term and long term).
- Drug-drug interactions, including with other existing and newly developed TB drugs and ARVs.
- Impact on mortality (including cause of death).
- Acquisition of resistance to bedaquiline and to other TB drugs.
- Duration and dosing of treatment.
- Patients’ values.
- Further research on the validity of culture conversion as a surrogate marker of treatment outcome.
Live use of iEtDs

EtDs are shared with panel members before the meeting and online:

Clarify the process

During the preparation for input on the evidence (all members including conflicted members could be involved)

For initial agreement on the included evidence and additional considerations

If possible, feasible and appropriate for agreement on judgments for specific decision criteria (but may all happen at an in-person meeting)

Final draft EtDs before a final meeting
Review of previous judgments and update through online tool
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.

Results were ambiguous in low-income settings, and highly dependent on the assumptions made about the generalizability of trial results to routine settings. The expert group noted that further analysis would be needed to test the robustness of the assumptions in various settings and to separately assess affordability [1].
European Commission Initiative on Breast Cancer and ARIA (allergy)

Live decision-making for guidelines
Presentation formats of recommendations
EC Initiative on Breast Cancer (ECIBC)
Guidelines and Quality Assurance scheme for Breast Cancer

The European Commission, in response to the Council of the European Union's conclusions on reducing the burden of cancer, initiated a ground-breaking initiative to develop a European quality assurance scheme. This initiative, known as the European Commission Initiative on Breast Cancer (ECIBC), aims to improve the quality of breast cancer care across Europe through the implementation of evidence-based guidelines. The initiative emphasizes the importance of consistent and high-quality care, ensuring that patients receive the best possible treatment. Through collaboration and standardization, ECIBC seeks to enhance the overall effectiveness of breast cancer management, thereby contributing to improved outcomes for patients.
Breast Cancer screening recommendations for different age groups by the European Commission

For asymptomatic women aged **40 to 44** with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) **suggests not implementing mammography screening** (conditional recommendation, moderate certainty in the evidence).

For asymptomatic women aged **45 to 49** with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) **suggests mammography screening** over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence).

For asymptomatic women aged **50 to 69** with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) **recommends mammography screening** over no mammography screening, in the context of an organised screening programme (strong recommendation, moderate certainty in the evidence).

For asymptomatic women aged **70 to 74** with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) **suggests mammography screening** over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence).
**Question**

Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged of 50 to 69?

**Population:** Women aged of 50 to 69

**Intervention:** organised mammography screening

**Comparison:** no mammography screening

**Main outcomes:** Breast cancer mortality (short case accrual); Breast cancer mortality (longest case accrual available); All-cause mortality; Other cause mortality; Stage II breast cancer or higher; Stage III breast cancer or tumour size ≥40 mm; Rate of mastectomies; Provision of chemotherapy; Overdiagnosis (long case accrual); Quality of life (inferred from psychological effects); False-positive related adverse effects (psychological distress); and False-positive related adverse effects (biopsies and surgeries).

**Background:** Although mammography screening has both potential benefits and harms many countries have organised programmes for women aged 50 or older. A reassessment of the evidence for screening women aged 50 to 69 is appropriate considering advances in diagnosis and treatment of breast cancer.

**Management of Conflicts of Interests (Col):** Cols of all Guideline Development Group (GDG) members were assessed and managed by the Joint Research Centre (JRC) following an established procedure in line with European Commission rules. GDG member participation in the development of the recommendations was restricted, according to Col disclosure. Consequently for this particular question, the following GDG members were recused from voting: Mireille Broeders, Roberto d’Amico, Jan Danes, Patricia Fitzpatrick, Axel Gräwingholt, Elsa Pérez Gómez, Ruben van Engen, Cary van Landsveld-Verhoeven, and Kenneth Young.


**Assessment**

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the problem a priority?</strong></td>
<td>No</td>
<td>Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012—accounting for 25% of all cancers (GLOBE/CAN 2012). Breast cancer ranks as the fifth leading cause of cancer death worldwide and the second leading cause of cancer-related death in developed regions (citation). In the European Union, 367,090 women were diagnosed with breast cancer and 92,000 women died from the disease in 2012 (Ferlay 2013). Breast cancer ranks fourth among the top five cancers with the highest disease burden (Tsi脱落is 2016).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probably no</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probably yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Online interaction of panel

Send EtD frameworks for individual voting to panel members. Voting can be run in one or two phases. Voting consists of one phase if you decide to send all parts of EtD framework (Assessment, Type of recommendation, Conclusions) at once. Voting consists of two phases if you decide to send parts of EtD framework separately.

Please decide what should be sent in phase 1:

1. Do you want to send proposed judgments for voting in Assessment part of EtD framework? (See examples of panel members’ voting form - judgments)
   - All judgments proposed (panel members vote agree/disagree)
   - None judgments proposed (panel members vote on full scale)
   - Some judgments proposed (panel member vote agree/disagree or on full scale)

2. Which parts of EtD (Assessment, Type of recommendation, Conclusions) do you want to send in phase 1? (See examples of panel members’ voting form - parts of EtD)
   - Only Assessment
   - Assessment and Type of recommendation (empty)
   - Assessment (proposed) and Type of recommendation (proposed) and Conclusions (proposed)

3. Which questions do you want to send?
   Please note that in order to send an EtD framework, all of the required data should be filled in.
   - Select all

- Should altered fractionation vs. conventional radiotherapy be used for asthma prevention?
- Should SOTI vs. elimination diet be used for asthma prevention?
- Should ICS vs. ICS+LABA be used for asthma prevention?

Compared to placebo
- Should SOTI vs. placebo be used for asthma prevention?
Online agreement
Online agreement
cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).

## Desirable Effects: How substantial are the desirable anticipated effects?

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>YOUR JUDGMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESIRABLE EFFECTS:</td>
<td>Trivial</td>
<td>The relative importance or values of the main outcomes of interest:</td>
</tr>
<tr>
<td>How substantial are</td>
<td>Small</td>
<td>SoF table</td>
</tr>
<tr>
<td>the desirable anticipated</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>effects?</td>
<td>Large</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don't know</td>
<td></td>
</tr>
</tbody>
</table>

**Comment:**
Provide a reason for your decision or other comments.

---

## Undesirable Effects: How substantial are the undesirable anticipated effects?

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>YOUR JUDGMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNDESIRABLE EFFECTS:</td>
<td>Trivial</td>
<td>The relative importance or values of the main outcomes of interest:</td>
</tr>
<tr>
<td>How substantial are</td>
<td>Small</td>
<td>SoF table</td>
</tr>
<tr>
<td>the undesirable anticipated</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>effects?</td>
<td>Large</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don't know</td>
<td></td>
</tr>
</tbody>
</table>

**Comment:**
Provide a reason for your decision or other comments.

---

Voting on "Assessment" part when judgments are empty.
**Question:** Should ICS vs. ICS+LABA be used for asthma prevention?

**Population:** Adults with asthma

**Intervention:** ICS

**Comparison:** ICS+LABA

**Main outcomes:** Any AE (95% CI); Any AE (99% CI); Any AE (90% CI);

**Setting:** Global

**Perspective:** Patient

### Evidence to Decision framework

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>PROPOSED JUDGMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROBLEM: Is the problem a priority?</strong></td>
<td>No</td>
<td>AR is a worldwide common disease in children and adolescents. Although the great majority of the cases begin during childhood, its prevalence changes throughout the life. The overall prevalence of AR is 14.6% (range 10.1 to 24.5%) in 13-14 years old children, and for the 6 to 7 years old children is 8.5% (range 4.2-12.7%) (Ait-Khaled 2009). Some studies have shown that the overall prevalence in adult patients AR clinically confirmed is between 17% to 30%, with an overall value of 23% in Europe (Bauchau 2004, Cingi 2010), a range between 8 to 21% in China (Zhang 2009), and approximately 7% in Latin America (Izquierdo 2013). The distribution of SAR vs Perennial is more difficult to estimate because it varies among studies and among countries, being similar in some countries, while in others they are not. In the United States it has been estimated that 20% of cases are SAR, 40% of cases are perennial rhinitis, and 40% of cases are mixed (Skoner 2001).</td>
</tr>
</tbody>
</table>

**Comment**  
Provide a reason for your decision or other comments

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>PROPOSED JUDGMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DESIRABLE EFFECTS: How substantial are the desirable anticipated effects?</strong></td>
<td>Trivial</td>
<td>The relative importance or values of the main outcomes of interest:</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>SoF table</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td></td>
</tr>
</tbody>
</table>

Comment  
Provide a reason for your decision or other comments
If you are aged 40 to 44, should you attend an organised mammography screening programme?

Recommendation

The ECIBC guidelines suggest not providing mammography screening to women between 40 and 44 years old who are at average risk of breast cancer and do not have symptoms.

Recommendation strength

Conditional recommendation against the intervention*
Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 40 to 44?

**Recommendation**

For asymptomatic women aged 40 to 44 with an average risk of breast cancer, the ECIBC’s Guidelines Development Group (GDG) suggests not implementing mammography screening. This is a **conditional recommendation**, with moderate certainty in the evidence.

**Recommendation strength**

Conditional recommendation against the intervention*
**Question**

Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged of 50 to 69?

**Assessment**

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the problem a priority?</td>
<td>Yes</td>
<td>Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012—accounting for 25% of all cancers (GLOBOCAN 2012). Breast cancer ranks as the fifth leading cause of cancer death worldwide and the second leading cause of cancer-related death in developed regions (citation). In the European Union, 367,090 women were diagnosed with breast cancer and 92,000 women died from the disease in 2012 (Ferlay 2013). Breast cancer ranks fourth among the top five cancers with the highest disease burden (Tsiliidou 2016). Annual incidence of breast cancer in the EU among women aged 50 to 69 is 2.7 per 1,000 and mortality is 0.5 per 1,000 (GLOBOCAN 2012)</td>
<td>These studies used an 'intention-to-treat' analysis thus, a per protocol approach would lead to even larger absolute effects. Estimates from observational studies were similar to those described here (see evidence profile). As there was disagreement among GDG members regarding whether the effects were large or moderate, voting took place among the 18 GDG members: 15 GDG members voted that the effects were large. Two GDG members voted that the effects were moderate. One</td>
</tr>
<tr>
<td>How substantial are the desirable anticipated effects?</td>
<td>Large</td>
<td>Six trials of invitation to mammography screening provided breast cancer mortality data from 249,160 women aged 50 to 69 (short case accrual). Mammography (using short case accrual), compared to no screening, reduced the risk of breast cancer mortality (Relative Risk (RR) = 0.76, 95% CI 0.64-0.90; Inconsistency (I²) = 52%, p = 0.06) (high quality evidence). This translates into an absolute effect of 144 fewer breast cancer deaths per 100,000 women invited to screening over 18 years (range: 60 to 216 fewer deaths). Mammography screening also reduced breast cancer mortality using 'longest case accrual available' (RR = 0.78, 95% CI 0.67-0.90; I² = 54%, p = 0.05; resulting in 167 fewer breast cancer deaths per 100,000 women over 17.3 years, from 76 to 251 fewer) (high quality evidence) and stage III+ breast cancer or tumour size ≥ 40 mm in diameter.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer?

**How substantial are the undesirable anticipated effects?**
- Large
- Moderate
- Small
- Trivial
- Varies
- Don’t know

**Detailed judgements**

Overdiagnosis from two randomised clinical trials (RCTs) were 10.1% (95% CI 8.6%-11.6%; I²=0%, p=0.61) (moderate quality evidence) from a population perspective (long case accrual). From the perspective of women invited to screening, the proportion of overdiagnosed women was 17.3% (95% CI 14.7-20.0; I²=10%, p=0.29) (moderate quality evidence).

Mammography screening compared with no screening did not increase the number of women aged 43 to 74 treated with chemotherapy (RR=0.86, 95% CI 0.52-1.41; I²=71%, p=0.06) (very low quality evidence). A systematic review of observational studies (Brett 2005) reported that women who had further testing following their routine mammogram experienced significant short term anxiety.

A systematic review by Hofvind (2012), reported estimated cumulative risk of a false-positive screening result in women aged 50 to 69 undergoing 10 biennial screening tests was 19.7%. In addition, the EUNICE Project showed that 2.2% of women had a needle biopsy after an initial screening mammogram. False-positive mammograms are also associated with greater anxiety and distress about breast cancer (Salz 2010). Furthermore, the negative psychological consequences may last up to three years (Bond 2013) (low quality evidence).

**What is the overall certainty of the evidence of effects?**
- Very low
- Low
- Moderate
- High

The overall certainty (i.e. quality) of the evidence was moderate, as this was the lowest quality (corresponding to the quality of the evidence for overdiagnosis) of the two critical outcomes – namely, breast cancer mortality and overdiagnosis.

Effects of chemotherapy and mastectomy were not considered to change the recommendation, and thus did not critically influence the overall certainty in the evidence.
Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer?

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 important uncertainty or variability

A systematic review (JRC Technical Report PICO 10-11, contract FWC443094012015; available upon request) shows that women placed little value on the psychosocial and physical effects of false-positive results and overdiagnosis. However, women generally consider these undesirable effects acceptable (low confidence in evidence). These findings are of limited value mainly given the significant concerns regarding the adequacy of the information provided to the participants, in order to make an informed decision. Another finding is that breast cancer screening represents a significant burden for some women due to associated psychological distress and inconvenience (moderate confidence in evidence).

Also, acceptability of false-positive results is based on studies of patients who have already received a false-positive result and, whose preferences may differ from the general population.

Regarding breast cancer diagnosis, very limited data is available addressing patients’ views. One of the main themes identified in the literature is that patients have a high disregard for anxiety caused by delays in receiving diagnostic results from or by a lack of understanding of the tests due to suboptimal communication with physicians (moderate confidence in evidence). Also, women have a higher overall preference towards more comfortable, brief diagnostic procedures (moderate confidence in evidence).
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 important uncertainty or variability

Detailed judgements

The relative importance of the outcomes is as follows:
- Pulmonary embolism: 0.63-0.93
- Deep vein thrombosis: 0.64-0.99
- Deep vein thrombosis patients’ own current health: 0.95 (Time trade off)

Patients highly value the benefits of VTE risk reduction of VTE prophylaxis; patients would like to avoid adverse events but most of them are “not afraid of” the adverse events.

For patients using mechanical methods to prevent VTE, in general patients would like to continue with the same methods. However, discomfort with the mechanical methods is a major complaint with this intervention. Most patients prefer knee-length stockings rather than thigh-length stockings.

The tolerability of the stockings was described as very good with no complaints of side effects. None of the other trials reported adverse effects of wearing the stockings (Clarke et al., 2016). For patients using any mechanical methods to prevent VTE, in general, they would like to continue with the same methods. Most patients prefer knee-length stockings rather than thigh-length stockings.
The panel evaluated the effects of screening.
56 fewer breast cancer deaths per 100,000 women but 12,400 false positives per 100,000 women with related consequences
### Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 50 to 69?

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>Summary of Judgements</th>
<th>FAVORS (no mammography vs. mammography)</th>
<th>INFORMING DECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROBLEM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Possibly yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>DESIRABLE EFFECTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UNDESIRABLE EFFECTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CERTAINTY OF EVIDENCE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VALUES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Important uncertainty in...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly important...</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BALANCE OF EFFECTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favors the comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RESOURCES REQUIRED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COST EFFECTIVENESS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favors the comparison</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EQUITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACCEPTABILITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FEASIBILITY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions

**Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 50 to 69?**

For asymptomatic women aged 50 to 69 with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) recommends mammography screening over no mammography screening, in the context of an organised screening programme (strong recommendation, moderate certainty in the evidence).
What about younger women

For asymptomatic women aged 40 to 44 with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) suggests not implementing mammography screening (conditional recommendation, moderate certainty in the evidence).

For asymptomatic women aged 45 to 49 with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence).

For asymptomatic women aged 50 to 69 with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) recommends mammography screening over no mammography screening, in the context of an organised screening programme (strong recommendation, moderate certainty in the evidence).

For asymptomatic women aged 70 to 74 with an average risk of breast cancer, the ECIBC’s Guideline Development Group (GDG) suggests mammography screening over no mammography screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence).
### Summary of judgements

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>PROBLEM</th>
<th>DESIRABLE EFFECTS</th>
<th>UNDESIRABLE EFFECTS</th>
<th>CERTAINTY OF EVIDENCE</th>
<th>VALUES</th>
<th>BALANCE OF EFFECTS</th>
<th>RESOURCES REQUIRED</th>
<th>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</th>
<th>COST EFFECTIVENESS</th>
<th>EQUITY</th>
<th>ACCEPTABILITY</th>
<th>FEASIBILITY</th>
<th>SUMMARY OF JUDGEMENTS</th>
<th>FAVORS mammography screening</th>
<th>FAVORS no mammography screening</th>
<th>IMPORTANCE FOR DECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of benefit</td>
<td>No</td>
<td>Trivial</td>
<td>Large</td>
<td>Very low</td>
<td>Important uncertainty</td>
<td>Favors the comparison</td>
<td>High costs</td>
<td>Very low</td>
<td>Favors the intervention</td>
<td>Reduced</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Probability of harm</td>
<td>No</td>
<td>Small</td>
<td>Moderate</td>
<td>Low</td>
<td>Possibly important...</td>
<td>Possibly favors the...</td>
<td>Moderate costs</td>
<td>Low</td>
<td>Does not favor either the...</td>
<td>Probably reduced</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Probability of bias</td>
<td>No</td>
<td>Moderate</td>
<td>Small</td>
<td>Low</td>
<td>Important uncertainty</td>
<td>Probable no bias</td>
<td>Moderate costs</td>
<td>Moderate</td>
<td>Favor the intervention</td>
<td>Increased</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Probability of acceptability</td>
<td>No</td>
<td>Large</td>
<td>Moderate</td>
<td>High</td>
<td>No</td>
<td>Probability of acceptability</td>
<td>Negligible costs</td>
<td>No included studies</td>
<td>Does not favor either the...</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Probability of feasibility</td>
<td>No</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>No</td>
<td>Probability of feasibility</td>
<td>Large costs</td>
<td>No included studies</td>
<td>Favor the intervention</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

### Conclusions

Should organised mammography screening vs. no mammography screening be used for early detection of breast cancer in women aged 40 to 44?

**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**

For asymptomatic women aged 40 to 44 with an average risk of breast cancer, the ECBC's Guidelines Development Group (GDG) suggests not implementing mammography screening (conditional recommendation, moderate certainty in the evidence).
American Society of Hematology

Panelvoice
• Online interaction, voting, consensus, public comment

Health Marker States
Semi-automated development of interactive decision aids
The American Society of Hematology and McMaster University Announce Partnership to Develop Clinical Practice Guidelines on Venous Thromboembolism

Guidelines on the Treatment and Diagnosis of VTE Anticipated in 2017

(WASHINGTON, November 30, 2015) – The American Society of Hematology, the world’s largest association of clinicians and scientists dedicated to conquering blood diseases, is collaborating with McMaster University, a world leader in guideline development and an international authority on thrombosis, to develop clinical practice guidelines on the diagnosis and treatment of venous thromboembolism (VTE).

VTE is a blood clotting disorder that includes both deep-vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a blood clot
In-person and teleconference meetings
Learning how to make recommendations: in-person meeting
Follow-up work: online interaction and teleconferences
Helps with deciding about degree of discussion needed
Helps with deciding about degree of discussion needed
**Comments**

**DESIRABLE EFFECTS:** How substantial are the desirable anticipated effects?

**DRAFT JUDGEMENT:** Small

Team members' votes and comments

**TRIVIAL**
Frederick **Spencer, Suely Rezende**

**SMALL**
Mary **Cushman, Allison Burnett**

**MODERATE**
Susan **Kahn**
Moderate based on relative effect and absolute risk difference primarily driven by mortality outcome, (but hesitant re low quality of evidence and imprecision)

**Jill Lansing**

**DON'T KNOW**
Neil **Zakai**
This study is not robust enough to address the issue.

**Summary**
Trivial 29% Small 29% Moderate 29% Large 0% Don't know 14%

Comments;
Moderate based on relative effect and absolute risk difference primarily driven by mortality outcome, (but hesitant re low quality of evidence and imprecision) This study is not robust enough to address the issue.
Comment from moderator: we are not addressing certainty in the evidence here. This will come under that criterion and when balancing benefits and harms.
Most recommendations
Will be conditional
 Require support with implementation
GRADE Conditional/weak recommendations

Patients/people: The majority of people in this situation would want the recommended course of action, but many would not.

Clinicians: Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making are useful.

Policy makers/QA: There is a need for substantial debate and involvement of stakeholders. Performance measures should assess if decision-making appropriate.
COMMENTARY

Clinical practice guidelines and patient decision aids. An inevitable relationship

Trudy van der Weijden\textsuperscript{a,b,*}, Antoine Boivin\textsuperscript{b,c}, Jako Burgers\textsuperscript{b}, Holger J. Schünemann\textsuperscript{d,e}, Glyn Elwyn\textsuperscript{b,f}

\textsuperscript{a}Department of General Practice, CAPHRI School of Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands
\textsuperscript{b}Department IQ Healthcare, Scientific Institute for Quality of Healthcare, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
\textsuperscript{c}Agence de la santé et des services sociaux de l’Abitibi-Témiscamingue, Rouyn-Noranda, Quebec, Canada
\textsuperscript{d}Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
\textsuperscript{e}Department of Medicine, McMaster University, Hamilton, Ontario, Canada
\textsuperscript{f}Clinical Epidemiology Interdisciplinary Research Group, Department of Primary Care and Public Health, School of Medicine, Cardiff University, Heath Park, Cardiff, UK

Accepted 2 October 2011; Published online 31 January 2012
Should patients with unprovoked (no reason found) deep venous thrombosis receive up to 12 months or lifelong anticoagulation?

The ASH guideline panel suggests using indefinite duration of antithrombotic therapy over defined duration antithrombotic therapy (12 months or less) in patients with unprovoked DVT/PE (conditional recommendation based on moderate certainty in the evidence about effects).
GRADE decision criteria
Values

Treatment
5% fewer death from PE
1% fewer death from PE

Comparison
5% more small bleeds
99% more small bleeds
Clinical Practice Guideline

Decision points:

- Low uncertainty / Strong recommendation (e.g. aspirin use in myocardial infarction)
- High uncertainty / Conditional recommendation (e.g. lumpectomy Vs mastectomy in breast ca)

Supporting optimal behaviors

INFORMATION COMPONENTS
- Define clear recommendation
- Communicate benefits and risks to explain the rationale

BEHAVIOR CHANGE COMPONENTS
- Implementation strategies
- Performance measures based on professional/patient behavior
  (prescribing aspirins/ taking aspirins)

Supporting deliberation

INFORMATION COMPONENTS
- Make options explicit
- Communicate benefits and risks of options to explain the dilemma

DECISION MAKING COMPONENTS
- Deliberation methods
- Preference constructing methods
- Performance measures based on quality of decision process (e.g. use of breast cancer decision aid)
Three general ways of supporting patients’ decisions

1. Inform and let patient walk off and make decision by themselves
2. Inform patient but asks for decision to be made by others
3. Inform and share decision
GRADE-based interactive Decision Aids
INTRODUCTION

Inhaled steroids present a treatment option for Chronic Obstructive Pulmonary Disease (COPD). Inhaled steroids have some of benefits, but they come with certain downsides. That's why deciding whether to use inhaled steroids or not will depend on each individual's values.

If a clinician has told you that inhaled steroids are a possible treatment option for you this Decision Aid can help you decide whether to use inhaled steroids or not.

We believe that your participation in making this treatment decision about your health is very important. However, the degree to which you actively participate in making this decision is up to you.
What you should remember?

Problem
Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) are major contributors to global disease burden. Their estimated incidence range from 0.7 to 2.7 per 1000 patients-year in Western Europe, 1.1 to 2.4 per 1000 patients-year in North America, and 0.8 to 1.2 per 1000 patients-year in Japan.

Myths and Facts
Deep Vein Thrombosis (DVT) is a blood clot that forms in a major vein of the leg or, less commonly, in the arms.
Should indefinite duration of Antithrombotic Therapy vs. defined duration (12 months or less) Antithrombotic Therapy be used in patients with unprovoked DVT/PE?

### COMPARISON

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Defined duration (12 months or less) Antithrombotic Therapy</th>
<th>Indefinite duration of Antithrombotic Therapy</th>
<th>Events per 1000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>18 follow-up mean 28 months</td>
<td>4 fewer (6 fewer to 2 more)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Moderate PE</td>
<td>28 follow-up mean 24 months</td>
<td>20 fewer (24 fewer to 14 fewer)</td>
<td>High</td>
</tr>
<tr>
<td>All DVT</td>
<td>58 follow-up mean 24 months</td>
<td>46 fewer (51 fewer to 39 fewer)</td>
<td>Low</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 follow-up mean 28 month</td>
<td>9 more (3 more to 16 more)</td>
<td>Low</td>
</tr>
</tbody>
</table>

### EXPERTS RECOMMENDATION

**WEAK RECOMMENDATION**

The ASH guideline panel suggests using indefinite duration of antithrombotic therapy over defined duration antithrombotic therapy (12 months or less) in patients with unprovoked DVT/PE (conditional recommendation based on moderate certainty in the evidence about effects).

**Remarks:**

The majority of the panel felt that most patients with an unprovoked VTE would benefit from indefinite anticoagulant therapy. However, this needs to include a careful assessment of risks and benefits for the individual patient and the patient’s preferences, as well as a regular re-evaluation of these parameters.
### Should an indefinite duration of antithrombotic therapy vs. a defined duration (12 months or less) be used in patients with unprovoked DVT/PE?

An indefinite duration of antithrombotic therapy compared to a defined duration (12 months or less) in patients with unprovoked DVT/PE.

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (follow up: mean 28 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 1234567890123</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>44/5877 (1.1%)</td>
<td>An indefinite duration of antithrombotic therapy</td>
<td>RR 0.75</td>
<td>5 fewer per 1,000 (from 2 more to 9 fewer)</td>
</tr>
<tr>
<td><strong>Moderate PE (follow up: mean 24 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 1234567890123</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>33/4138 (0.8%)</td>
<td>A defined duration (12 months or less)</td>
<td>RR 0.29</td>
<td>21 fewer per 1,000 (from 13 fewer to 25 fewer)</td>
</tr>
<tr>
<td><strong>ALL DVT (follow up: mean 24 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 1234567890123</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>50/4185 (1.2%)</td>
<td></td>
<td>RR 0.20</td>
<td>50 fewer per 1,000 (from 42 fewer to 16 fewer)</td>
</tr>
<tr>
<td><strong>ALL DVT - DOAC (follow up: mean 24 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 1234567890123</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>31/3548 (0.9%)</td>
<td></td>
<td>RR 0.15</td>
<td>49 fewer per 1,000 (from 44 fewer to 51 fewer)</td>
</tr>
<tr>
<td><strong>ALL DVT - VKA/LMWH (follow up: mean 24 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 1234567890123</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>5/412 (0.7%)</td>
<td></td>
<td>RR 0.17</td>
<td>54 fewer per 1,000 (from 50 fewer to 61 fewer)</td>
</tr>
<tr>
<td><strong>All DVT - Aspirin (follow up: mean 24 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>16/205 (0.8%)</td>
<td></td>
<td>RR 0.55</td>
<td>64 fewer per 1,000 (from 5 fewer to 98)</td>
</tr>
</tbody>
</table>
### Should an indefinite duration of antithrombotic therapy vs. a defined duration (12 months or less) be used in patients with unprovoked DVT/PE?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Absolute Effect Without an indefinite duration of antithrombotic therapy</th>
<th>Absolute Effect With an indefinite duration of antithrombotic therapy</th>
<th>Certainty of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>18 per 1000 patients</td>
<td>14 per 1000 patients</td>
<td>GRADE Moderate</td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference: 4 fewer per 1000 patients (95% CI: 2 to 6 fewer per 1000 patients) Based on data from 6,951 patients in 10 studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate PE</strong></td>
<td>29 per 1000 patients</td>
<td>8 per 1000 patients</td>
<td>GRADE High</td>
</tr>
<tr>
<td>Follow-up: 24 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference: 21 fewer per 1000 patients (95% CI: 12 to 31 fewer per 1000 patients) Based on data from 7,840 patients in 9 studies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**All DVT** Follow-up: 24 months

**All DVT - DOAC** Follow-up: 24 months

**All DVT - VKA/LMWH** Follow-up: 24 months

**All DVT - Aspirin** Follow-up: 24 months

**Major bleeding** Follow-up: 26 months
Should an indefinite duration of antithrombotic therapy vs. a defined duration (12 months or less) be used in patients with unprovoked DVT/PE?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Absolute Effect</th>
<th>Differences in outcomes</th>
<th>Certainty of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>Without an indefinite duration of antithrombotic therapy</td>
<td>With an indefinite duration of antithrombotic therapy</td>
<td>Favour an indefinite duration of antithrombotic therapy</td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>18 per 1000</td>
<td>14 per 1000</td>
<td>4 fewer per 1000 patients</td>
</tr>
<tr>
<td></td>
<td>Difference: 4 fewer per 1000 patients (95% CI: 1 to 7 fewer per 1000 patients) based on data from 6951 patients in 10 studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate PE</strong></td>
<td>Follow-up: 24 months</td>
<td>Study population</td>
<td>Unprovoked Event - 1 year</td>
</tr>
<tr>
<td></td>
<td>29 per 1000</td>
<td>8 per 1000</td>
<td>21 fewer per 1000 patients</td>
</tr>
<tr>
<td></td>
<td>Difference: 21 fewer per 1000 patients (95% CI: 15 to 25 fewer per 1000 patients) based on data from 7440 patients in 9 studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Should an indefinite duration of antithrombotic therapy vs. a defined duration (12 months or less) be used in patients with unprovoked DVT/PE?

#### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Absolute Effect</th>
<th>Relative Effect</th>
<th>Visual overview</th>
<th>Relative Effect</th>
<th>Certainty of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>18 per 1000</td>
<td></td>
<td></td>
<td>RR 0.75</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Moderate PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>29 per 1000</td>
<td></td>
<td></td>
<td>RR 0.29</td>
<td>High</td>
</tr>
<tr>
<td><strong>All DVT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>5 per 1000</td>
<td></td>
<td></td>
<td>RR 2.24</td>
<td>High</td>
</tr>
<tr>
<td><strong>All DVT - DOAC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>11 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All DVT - VKA/LMWH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>11 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All DVT - Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 28 months</td>
<td>11 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Differences in outcomes**

- **Mortality**
  - Without an indefinite duration of antithrombotic therapy: 18 per 1000
  - With an indefinite duration of antithrombotic therapy: 14 per 1000
  - Difference: 4 fewer per 1000 patients

- **Moderate PE**
  - Without an indefinite duration of antithrombotic therapy: 29 per 1000
  - With an indefinite duration of antithrombotic therapy: 8 per 1000
  - Difference: 21 fewer per 1000 patients

- **All DVT**
  - Without an indefinite duration of antithrombotic therapy: 5 per 1000
  - With an indefinite duration of antithrombotic therapy: 11 per 1000
  - Difference: 6 more per 1000 patients

**Relative effect**

- **Mortality**
  - RR 0.75 (0.49 to 1.15)

- **Moderate PE**
  - RR 0.29 (0.13 to 0.56)

- **All DVT**
  - RR 2.24 (1.49 to 3.30)

**Certainty of the evidence**

- **Mortality**: Moderate
- **Moderate PE**: High
- **All DVT**: High
The ASH guideline panel suggests using indefinite duration of antithrombotic therapy over defined duration antithrombotic therapy (12 months or less) in patients with unprovoked DVT/PE (conditional recommendation based on moderate certainty in the evidence about effects).

Remarks:
The majority of the panel felt that most patients with an unprovoked VTE would benefit from indefinite anticoagulant therapy. However, this needs to include a careful assessment of risks and benefits for the individual patient and the patient's preferences, as well as a regular re-evaluation of these parameters.
How important are the outcomes?
Your Values

Indicate the importance of each benefit and downside on a scale from 0 to 100, where 0 indicates the worst imaginable health state (we define it as “dead”) and 100 indicates the best imaginable health state.

For me **Mortality** is equivalent to:

![Mortality Scale](image)

For me having a **Moderate PE** is equivalent to:

![Moderate PE Scale](image)

For me having a **All DVT** is equivalent to:

![All DVT Scale](image)

For me having a **Major bleeding** is equivalent to:

![Major bleeding Scale](image)
Your Values

Indicate the importance of each benefit and downside on a scale from 0 to 100, where 0 indicates the worst imaginable health state (we define it as "dead") and 100 indicates the best imaginable health state.

For me **Mortality** is equivalent to:

0 10 20 30 40 50 60 70 80 90 100

For me having a **Moderate PE** is equivalent to:

0 10 20 30 40 50 60 70 80 90 100

For me having a **All DVT** is equivalent to:

0 10 20 30 40 50 60 70 80 90 100

For me having a **Major bleeding** is equivalent to:

0 10 20 30 40 50 60 70 80 90 100
For me Mortality is equivalent to:

For me having a Moderate PE is equivalent to:

For me having a All DVT is equivalent to:

For me having a Major bleeding is equivalent to:

Calculate your individual risk

Start
What is your baseline risk?
My Risk

Men

Age ≥ 65
No [ ] Yes [ ]

Hyperpigmentation
No [ ] Yes [ ]

Edema
No [ ] Yes [ ]

Redness
No [ ] Yes [ ]

D-dimer ≥250 µg/L during AC
No [ ] Yes [ ]

Women

Obesity (BMI ≥30 kg/m²)
No [ ] Yes [ ]
My Risk

Men       Women

Age ≥ 65
No    Yes

Hyperpigmentation
No    Yes

Edema
No    Yes

Redness
No    Yes

D-dimer ≥250 µg/L during AC
No    Yes

Obesity (BMI ≥30 kg/m²)
No    Yes

Total Risk: 2
Your general DVT risk is **14.2%**

It means that with indefinite duration of Antithrombotic Therapy 114 fewer (per 1000) patients like you experience DVT.

---

**General population results**

- **All DVT**
  - Follow-up mean: 24 months
  - 58 per 1000

- **46 fewer**
  - (51 fewer to 39 fewer)
  - High risk

**Your individual risk**

- **All DVT**
  - Follow-up mean: 24 months
  - 142 per 1000

- **114 fewer**
  - (135 fewer to 97 fewer)
  - High risk
Should Indefinite duration of Antithrombotic Therapy vs. defined duration (12 months or less) Antithrombotic Therapy be used in patients with unprovoked DVT/PE?

My reasons to have Defined duration (12 months or less) Antithrombotic Therapy:

- My risk of having **Major bleeding** reduced by 20 per 1000 cases: 54

My reasons to have Indefinite duration of Antithrombotic Therapy:

- My risk of **death** will be reduced by 4 in 1000 cases: 0
- My risk of having **PE** is reduced by 20 per 1000 cases: 30
- My risk of having **DVT** reduced by 114 per 1000 cases: 35

Less important outcomes

Have the Decision Aid balance the benefits and downsides for you and get...
Link to outcomes for panel and patients

Major Bleeding
(Bleeding with Substantial Blood Loss)

Importance

Utility

Symptoms
You lose a lot of blood (e.g. vomit blood, blood with your stools, blood from a wound) or you have an internal bleeding.

Time Horizon
Bleeding does not stop and you have to receive specific urgent care.

Testing and Treatment
You may require a CT scan, a flexible tube via your mouth or anus to investigate your bowel, and blood work, and you may be admitted to hospital to receive blood transfusion or surgery.

Consequences
You may recover completely, but you may instead have permanent neurological damage if your brain does not receive blood for an extended period of time (e.g. be unable to speak or understand, or wheel-chair bound), or even die.
Should Indefinite duration of Antithrombotic Therapy vs. defined duration (12 months or less) Antithrombotic Therapy be used in patients with unprovoked DVT/PE?

My reasons to have Defined duration (12 months or less) Antithrombotic Therapy:

- **Outcomes**: My risk of having **Major bleeding** reduced by 20 per 1000 cases
- **Importance rating**: 54

My reasons to have Indefinite duration of Antithrombotic Therapy:

- **Outcomes**:
  - My risk of **death** will be reduced by 4 in 1000 cases
  - My risk of having **PE** is reduced by 20 per 1000 cases
  - My risk of having **DVT** reduced by 114 per 1000 cases
- **Importance rating**: 30, 30, 35

Less important outcomes

Have the Decision Aid balance the benefits and downsides for you and get a recommendation. You can use this recommendation to make a decision.

See recommendation
Summary

1. GRADEpro – official tool of GRADE working group – linkage to GIN-Guideline checklist
2. Grading evidence and recommendations
3. Remote, web/browser-based interaction
4. Panel input, voting and consensus
5. Highly flexible and not prescriptive
6. Interactive Summary of Findings Tables (iSoF)
7. Interactive Decision Aids (iDA)
8. Adaptation, etc.