Integrity and Transparency of Decisions on Essential Medicines

Holger Schünemann, MD, MSc, PhD, FRCPC
Professor of Medicine and Clinical Epidemiology

WHO Collaborating Center for Infectious Diseases, Research Methods, McMaster University
Disclosures

• No direct financial conflicts
• GRADE Working Group Co-Chair
• Cochrane Canada - Director
• Guideline International Network – vice chair
• Research grants from Canadian Institutes of Health Research and WHO
• Consultant to WHO, MSIF
• Views expressed my own

Thanks to:
• T. Piggott (whose thesis work is instrumental for this presentation)!
• Theory of everything collaborators
• L. Moja, B. Huttner
Today’s talk

1. Considerations about transparency of EML selection by building on decision-making frameworks
2. Opportunities for how transparency may ensure integrity of the selection and how we can learn from other disciplines
Background

• We submitted an application for inclusion of new oral anticoagulants (direct oral anticoagulants/DOACs) in WHO EML 2015 – rejected: need in LMIC? Cost differential to alternatives (warfarin)?

• Higher cost medicines such as direct acting antivirals for hepatitis C are included, but cancer medicines of similar cost have not been included
Concerns about the EML – use of evidence and reporting

1) Search strategy, reasons for inclusion or exclusion of data
2) Target population, comparison groups, and outcomes of interest
3) Quantitative summaries of overall treatment effects for each comparison and outcome
4) Quality of supporting evidence
5) Conflicts of interest: reporting and management

Barbui & Purgato, 2014
Criticism of the EML process

WHO ON ESSENTIAL MEDICINES

The composition of WHO’s expert committee on essential medicines needs more scrutiny

Craig Walsh, health policy consultant
Ganar, Australian Capital Territory, Australia

Barbui and Purgato call for reforms to both the standard of applications to and the clarity of reporting of decisions by the World Health Organization expert committee on essential medicines. But they don’t go far enough. It isn’t just the decisions that need more scrutiny but the composition of the committee too.

We are told only that the committee is made up of experts, “appointed by the WHO director general,” who meet “every two years to review applications with expert assessors and decide which medicines are added or deleted.” Just try to find out from the WHO website who the committee members are before a committee meeting— as opposed to when the meeting report is published—let alone their qualifications, fitness for the role, or conflicts of interest. Why is there never a call for nominations to the committee? The list of current members smacks of concealment, the appointments process is opaque, and the decisions lack clarity. Transparency is its own reward. WHO should, indeed, try leading by example.

Competing Interests: None declared.

Viewpoint

October 24, 2022

Reforming the World Health Organization’s Essential Medicines List

Essential but Unaffordable

Thomas J. Hwang, MD1,2; Aaron S. Kesselheim, MD, JD, MPH2; Kerstin N. Vokinger, MD, PhD2,3

© BMJ Publishing Group Ltd 2014
JAMA. Published online October 24, 2022. doi:10.1001/jama.2022.19459
So how can one efficiently …

a) enhance the transparency in how medicines are included in the EML?

b) describe and manage any potential biases (including conflicts) that could influence the process?

c) foster practical use of the EML in settings different income settings and legal frameworks?

d) increase the efficiency in the preparation of applications?

2021 anti-PD1 inhibitor application from ESMO used a non-systematic summary of the evidence - a Cochrane review on the exact same question was published Dec. 2020 – the month the application was submitted.
A striking similarity to …

Practice guidelines and their history at WHO and other decision makers in health

Health Research Policy and Systems

Use of evidence in guideline development

Andrew D Oxman, John N Lavis, Atle Fre

Summary

Background WHO regulations, recommendations. However, the process of evidence (effects, process values), evidence-informed evidence particularly evidence of effects.

Review

Improving the use of research evidence in guideline development:

1. Guidelines for guidelines

Holger J Schünemann*1, Atle Fretheim2 and Andrew D Oxman2

Address: 1INFORMA, S.C. Epidemiologia, Istituto Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy and 2Norwegian Knowledge Centre for the Health Services, P.O. Box 7004, St. Olavs plass, N-0130 Oslo, Norway

Email: Holger J Schünemann* - hj@buffalo.edu; Atle Fretheim - atle.fretheim@nokc.no; Andrew D Oxman - oxman@online.no

* Corresponding author

Published: 21 November 2006


Received: 07 April 2006
Accepted: 21 November 2006
Learn from guideline science

The process from prioritization to a recommendation and decision is now largely transparent and “reproducible”
Evidence to decision frameworks to enhance transparency of the process and decision ... also for the EML

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

GRADE Working Group DECIDE project 2011 – 2015 with WHO, NICE & partners

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

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

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well-informed healthcare choices. 3. Evidence to decision frameworks for tests in clinical practice and public health
Original EtD Framework (allows tailoring)
Discuss evidence

**QUESTION**
Should Intermediate intensity anticoagulation, therapeutic intensity anticoagulation vs. prophylactic intensity anticoagulation be used in Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE?

**Population:** Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE

**Intervention:** Intermediate intensity anticoagulation, therapeutic intensity anticoagulation

**Comparison:** prophylactic intensity anticoagulation

**Main outcomes:** Mortality; Pulmonary Embolism - representing the moderate PE marker state; Proximal Deep Vein Thrombosis - representing the moderate proximal DVT marker state; Major Bleeding.

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

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivial</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td></td>
</tr>
<tr>
<td>Varies</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**
- **Mortality**: Baseline: 34 to 38 days.
  - Baseline: 236
  - Prophylactic: 184
- **Pulmonary embolism**: Baseline: 3 to 5 days.
  - Baseline: 98
  - Prophylactic: 10
- **Vascular thrombosis of the lower leg (Proximal Lower extremity (VTE))**: Baseline: 5 to 30 days.
  - Baseline: 84
  - Prophylactic: 260
- **Venous thrombosis of the leg (Lower extremity (VTE))**: Baseline: 5 to 30 days.
  - Baseline: 84
  - Prophylactic: 260

**Consensus of the evidence**

- **Mortality**: Very Low
- **Pulmonary embolism**: Very Low
- **Vascular thrombosis of the lower leg (Proximal Lower extremity (VTE))**: Very Low
- **Venous thrombosis of the leg (Lower extremity (VTE))**: Very Low

**ADDITIONAL CONSIDERATIONS**
- Baseline: Very low risk of bias: Due to strong design limitations.
- Prophylactic: Very low risk of bias: Due to strong design limitations.
QUESTION

Should Intermediate intensity anticoagulation, therapeutic intensity anticoagulation vs. prophylactic intensity anticoagulation be used in patients with COVID-19-related acute illness who do not have confirmed or suspected VTE?

- **Population:** Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE
- **Intervention:** Intermediate intensity anticoagulation, therapeutic intensity anticoagulation
- **Comparison:** Prophylactic intensity anticoagulation
- **Main outcomes:** Mortality; Pulmonary Embolism - representing the moderate PE marker state; Proximal Deep Vein Thrombosis - representing the moderate proximal DVT marker state; Major Bleeding;

**Desirable Effects**

**Judgement**

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

**Research Evidence**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Absolute Effect</th>
<th>Relative Effect</th>
<th>Consistency of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>236 per 1000</td>
<td>184 per 1000</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>98 per 1000</td>
<td>10 per 1000</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Deep Venous Thrombosis of the upper leg (Proximal Lower extremity DVT)</td>
<td>84 per 1000</td>
<td>260 per 1000</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>84 per 1000</td>
<td>260 per 1000</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
Make judgments

**QUESTION**

Should Intermediate intensity anticoagulation, therapeutic intensity anticoagulation or prophylactic intensity anticoagulation be used in Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE?

**Population:** Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE

**Intervention:** Intermediate intensity anticoagulation, therapeutic intensity anticoagulation

**Comparison:** Prophylactic intensity anticoagulation

**Main outcomes:** Mortality; Pulmonary Embolism - representing the moderate PE marker state; Proximal Deep Vein Thrombosis - representing the moderate proximal DVT marker state; Major Bleeding;

**Desirable Effects**

How substantial are the desirable anticipated effects?

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

**Research Evidence**

<table>
<thead>
<tr>
<th>JUDGEMENT</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>236 vs. 184</td>
<td>Absolute effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual overview</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>98 vs. 10</td>
<td>Absolute effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual overview</td>
</tr>
<tr>
<td>Deep Venous Thrombosis of the upper leg</td>
<td>84 vs. 260</td>
<td>Absolute effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual overview</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>84 vs. 260</td>
<td>Absolute effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual overview</td>
</tr>
</tbody>
</table>
Make judgments

No conflicts of interest

QUESTION

Should Intermediate intensity anticoagulation, therapeutic intensity anticoagulation or prophylactic intensity anticoagulation be used in Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE?

Population: Patients with COVID-19-related acute illness who do not have confirmed or suspected VTE

Intervention: Intermediate intensity anticoagulation, therapeutic intensity anticoagulation

Comparison: Prophylactic intensity anticoagulation

Main outcomes: Mortality; Pulmonary Embolism - representing the moderate PE marker state; Proximal Deep Vein Thrombosis - representing the moderate proximal DVT marker state; Major Bleeding;

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

Additional Considerations

There was consensus among the panel that there was moderate harm with the intervention, with an increase in major bleeding as an undesirable effect.

There was no direct evidence available on the effects of the intervention and comparison on the following outcomes, which were also identified as priorities by the panel: Multiple Organ Failure; Ischemic stroke (severe); Intracranial hemorrhage; Invasive ventilation; Limb amputation; ICU hospitalization (duration); and ST-elevation myocardial infarction.
Decision criteria for selecting essential medicines and their connections to guidelines: an integrative descriptive qualitative interview study

Piggott et al., 2023
2021 EML Applications

Application for the inclusion of the anti-PD1 immune-checkpoint inhibitors in the WHO Model list of ESSENTIAL MEDICINES for the treatment of “non-oncogene- addicted” (EGFR, ALK, and ROS1 wild type) locally advanced and metastatic non-small cell lung cancer (NSCLC).

List of Contributors: George Penthoudakis, MD PhD

1. Name of the focal point in WHO submitting or supporting the application

André Ibars, WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention (NVi).

2. Name of the organization(s) consulted and/or supporting the application

European Society for Medical Oncology (ESMO)
Question
- Details – PICO Subgroups
- Background and conflicts of interest

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

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

Presentation
- Group meeting processes & informing coverage decisions
- Database of decision frameworks
- Decision Aids, apps
Intent: Treatment and rehabilitation

The World Health Organization recommends treatment with nirmatrelvir-ritonavir.
WHO COVID19 Recommendations

Enter the keyword to search in recommendations

Recommendations Map  Recommendations List

Guidance on Implementation

Gateway to adaptation

WHO eTB Guidelines

A database of WHO recommendations for TB prevention and care

Search in recommendations

This website provides access to the latest WHO recommendations on all aspects of tuberculosis prevention and care. The user can search, filter and cross-tabulate the recommendations through built-in functions. For each individual recommendation one can also access key background information, such as the evidence summaries and the Guideline Development Group decisions underpinning it.

https://who.tuberculosis.recmap.org/
# Ledipasvir + sofosbuvir

## Indication
Chronic hepatitis C

### ICD11 code:
IE91.1

### Formulations:
Oral > Solid: 90 mg + 400 mg tablet

### EML status history:
First added in 2015 (TRS 994)

### Sex:
All

### Age:
Adolescents and adults

### Therapeutic alternatives:
The recommendation is for this specific medicine

### Patent information:
Read more about patents

### Wikipedia:
Ledipasvir + sofosbuvir

### DrugBank:
Ledipasvir
Sofosbuvir
Evidence from Primary Research

Beyond guidelines: Evidence ecosystem of health decision-making

Questions in healthcare systems: Problem/Populations, Interventions, Comparators, and Outcomes (PICO)
Key visions for enhancing EML transparency

1. Improve the quality and evaluation of applications → EtD framework like process for all applications, rapid updating, cost-considerations?
2. Is it time to re-assess 2001 criteria for decision making (EB109/8): missing equity and feasibility (availability)?
3. Work with medicine funders to align financing with EML decision-making?
   - Move from comparative cost-effectiveness medication classes to affordability of medicines?
4. Strengthen the link with WHO guidelines and other norms and standards products → increase efficiency as there is much work to do
5. Work with the evidence-informed policy making to ensure essential medicine list decisions are translated into political priorities and policy decisions directly and indirectly
6. Improve dissemination and capacity building for both WHO and national EMLs
Summary

Little justification to do less than is demanded from guideline recommendations

- with regards to evidence to decision process, engagement and transparency to achieve integrity of the list

- consider the visions over the next days
Thank you


@schunemann_mac
schuneh@mcmaster.ca
In the meantime…

Examples of synergy between different decision-making bodies taught us how to enhance related processes:

Estonia national guideline making conditional recommendation for DOACs in atrial fibrillation – cost too high for strong recommendation based on systematic review and HTA

Price negotiations with Estonian Health Insurance Fund – manufacturer lowering price → strong recommendation

And, our repeat submission to the 2019 EML (directly based on our guideline with decision-making support) → Listing of DOACs, the evidence accumulated

- but did not change dramatically in terms of cost or need in LMIC
## Evidence to Decision Criteria:

### Different types of decisions

<table>
<thead>
<tr>
<th>Priority of the problem</th>
<th>Clinical recommendations - individual perspective</th>
<th>Clinical recommendations - population perspective</th>
<th>Coverage decisions</th>
<th>Health system and public health recommendations/decisions</th>
<th>Diagnostic, screening, and other tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Is the problem a priority?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test accuracy</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits and harms</td>
<td>How substantial are the desirable anticipated effects?</td>
<td>How substantial are the undesirable anticipated effects?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certainty of the evidence</td>
<td>What is the overall certainty of the evidence of effects?</td>
<td></td>
<td></td>
<td>What is the certainty of the evidence of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Test accuracy?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Any critical or important direct benefits, adverse effects, or burden of the test?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Effects of the management that is guided by the test results?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Link between test results and management decisions?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Effects of the test?</td>
<td></td>
</tr>
<tr>
<td>Outcome importance</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?</td>
<td></td>
<td></td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes, including adverse effects and burden of the test and downstream outcomes of clinical management that is guided by the test results?</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?</td>
<td></td>
<td></td>
<td>Does the balance between desirable and undesirable effects favour the test or the comparison?</td>
<td></td>
</tr>
<tr>
<td>Resource use</td>
<td></td>
<td></td>
<td></td>
<td>How large are the resource requirements (costs)?</td>
<td>Does the balance between desirable and undesirable effects favour the test or the comparison?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Does the cost effectiveness of the intervention (the out-of-pocket cost relative to the net benefits) favour the intervention or the comparison?</td>
<td>Does the balance between desirable and undesirable effects favour the test or the comparison?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Does the cost effectiveness of the intervention favour the intervention or the comparison?</td>
<td>Does the balance between desirable and undesirable effects favour the test or the comparison?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Does the cost effectiveness of the option favour the option or the comparison?</td>
<td>Does the balance between desirable and undesirable effects favour the test or the comparison?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Does the cost effectiveness of the test favour the test or the comparison?</td>
<td>Does the balance between desirable and undesirable effects favour the test or the comparison?</td>
</tr>
<tr>
<td>Equity</td>
<td></td>
<td></td>
<td></td>
<td>What would be the impact on health equity?</td>
<td></td>
</tr>
<tr>
<td>Acceptability</td>
<td>Is the intervention acceptable to patients, their caregivers, and healthcare providers?</td>
<td></td>
<td></td>
<td>Is the intervention acceptable to key stakeholders?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the intervention acceptable to key stakeholders?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the option acceptable to key stakeholders?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feasibility</td>
<td>Is the intervention feasible for patients, their caregivers, and healthcare providers?</td>
<td></td>
<td></td>
<td>Is the intervention feasible to implement?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the intervention feasible to implement?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the option feasible to implement?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the test feasible to implement?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Tests cover clinical and public health recommendations at individual and population perspectives.