Title

Supporting the Development of Trustworthy Essential Medicine Lists and their Synergy with Health Guidelines

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Lay Abstract

Medicines are important for treating health conditions, and the most important medicines are called essential medicines. Essential Medicine Lists (EMLs) are created to determine what should be considered an essential medicine around the world, and also to ensure people have access to them. The number of medicines on the World Health Organization's Model List of Essential Medicines (MLEM) has grown since it was first released, but these medicines aren't always available to treat people who need them. Sometimes medicines that are not the most important are included on national essential medicine lists. The way that the WHO EML and national EMLs are made has been under review and criticized. Health guidelines tell people how medicines should be used, however, the connection between EMLs and health guidelines is not always consistent. Sometimes they may say different things about the same medicine. Additionally, there are differences in how EMLs and guidelines are established, and those involved do not always work with each other. In this thesis, I try to understand how decisions about which medicines are included in EMLs are made, and how they connect to health guidelines. Chapter 1 is an introduction to the topic. Chapter 2 asks experts about the decision-making process for EMLs. In chapter 3, we change a tool for guidelines to help connect guideline and EML decisions and ask for feedback regarding improvements. Chapter 4 presents the work with a group of guideline experts to present problems and suggest ways to overcome them to make EMLs and health guidelines better connected.

Abstract

Essential Medicine Lists (EMLs) are important for the prioritization and availability of medicines around the world. Since the first Model List of Essential Medicines (MLEM) from the World Health Organization in 1977, the list has expanded from 208 to 479 medicines. The availability of essential medicines is a key priority under the World Health Organization's Universal Health Coverage agenda & the United Nation's Sustainable Development Goals (in particular goal 3.8 Coverage of Essential Health Services). EMLs are an important tool to inform health decisions at a country-level and at least 137 countries now have their own national EML. Despite this, there is wide variability in the methods used to develop them, and the certainty of evidence of medicines included on WHO's MLEM and national EMLs. Additionally, a lack of coordination may result in time delays in updating EMLs or unnecessary duplication of efforts between EMLs and other evidence synthesis and health decision-making paradigms, such as health guidelines. In this thesis, we seek to understand the decision-making process for EMLs with particular focus on WHO's MLEM, and to identify and advance opportunities to coordinate their development with health guidelines. This is accomplished through three papers, which build upon each other in this sandwich thesis. Paper 1 is a qualitative interview study with EML and guideline stakeholders to better understand decision-criteria and processes in EMLs. Paper 2 evaluates, using user-experience testing, a framework for the connection of guidelines and EMLs using an Evidence-to-Decision (EtD) framework for EMLs. Paper 3 presents a stakeholder-driven Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group

concept paper exploring the conceptual challenges and opportunities of linking guidelines and EMLs using case studies on real-world implementation of this connection.

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I would like to first and foremost thank my family for their support in my long journey in higher education which has (possibly?) culminated here. My parents inspired a curiosity and passion for equity and justice in me from the moment I could walk, and have always been there for me. My brother has been a trusted confidant and co-adventurer, helping me escape to the great outdoors where my creative thoughts could flow. My wife, Laura, has been my rock through many storms on the adventure of life. She has edited countless papers, engaged in reflective discussion and has been both my biggest critic and biggest cheerleader all at the same time. I am so fortunate and love her immeasurably. I'm grateful for my two little girls, who are my source of inspiration to make the world a healthier and better place for them to grow. I am also grateful for the support of my broader family and friend support system.

I have tremendous and eternal gratitude for the incredible journey and learning afforded to me by my supervisor, Dr. Holger Schünemann. Were it not for having been captivated through him by the wonderful world of guidelines, I would not have pursued a PhD. Dr. Schünemann had me enthralled in this research work from our first encounter at a guideline meeting in Geneva in 2015, and I have been excited and fascinated ever since. Every conversation, bicycle ride, and meeting we have had has inspired me and challenged me to think differently, grow, and give the best I can to improving health for people around the world through research. He has also modelled the balance between ensuring work is both meaningful and fun, a life lesson I will always hold.

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Finally, I would like to thank the many mentors along the way who I have been fortunate to have met, learn from and grown through. This is not an exhaustive list but some of my most influential are: Victoria, Alastair, Jacqueline, Neil, Montse, Mustafa, Jessica, Elizabeth, Howard, Linda, Heather, and Andy. They have taught me to not accept all as is and to fight to make the world a better place.

Thomas Piggott

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Preface

The work presented herein is composed of the papers constituting my sandwich thesis. The manuscript presented in chapter 2, “Decision Criteria for Selecting Essential Medicines and their Connection to Guidelines: An Interpretive Descriptive Qualitative Interview Study”, has been accepted for publication pending revision in the Journal of Clinical Epidemiology. The manuscript in chapter 3, “Chapter 3: User-Experience Testing of an Evidence-to-Decision Making Framework for Selecting of Essential Medicines” has been submitted to the journal PLoS Global Public Health and is currently being reviewed. The manuscript in chapter 4, “GRADE concepts: Linking Recommendations to Trustworthy Essential Medicine Lists”, is in a final draft form and in the process of being finalized and submitted for publication.

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List of Abbreviations

EML – Essential Medicines List

EtD – Evidence-to-Decision

GRADE - Grading of Recommendations Assessment, Development and Evaluation

HIREB – Hamilton Integrated Research Ethics Board

MSIF – Multiple Sclerosis International Federation

MEMP – Multiple Sclerosis Essential Medicines Panel

NEML – National Essential Medicines List

Declaration of Academic Achievement

I hereby declare that I, jointly with Professor Holger J. Schünemann as my supervisor, played the primary role in study conception, design, and execution of all studies included herein. We obtained feedback and input from Dr Lorenzo Moja, Professor John Lavis and Professor Elie Akl.

This work is original research that I have conducted. I am the first author and principal contributor to all manuscripts contained in this dissertation. I am responsible for the following in all manuscripts: design, conception and writing of materials. I have prepared all figures and tables. In chapter 2, I conducted all research and analysis of interviews, with feedback and analysis input from co-authors of this paper. In chapter 3, I conducted all interviews and analysis for user-experience testing. In chapter 4, I co-led the GRADE for Essential Medicines project group with Dr Lorenzo Moja and Professor Tamara Kredo; this involved chairing of meetings and supporting consensus on solutions identified. In Chapter 4, I was a Co-Chair for the MSIF MEMP guideline and supported this larger research/guideline endeavour. I wrote all manuscripts with editorial advice from Professor Schünemann, and feedback from Dr Lorenzo Moja, Professor John Lavis and Professor Elie Akl.

Chapter 1: Introduction

Background

Essential Medicines

Access to affordable essential medicines is a critical challenge globally. In countries aspiring to improvements in universal health coverage (UHC), essential medicines are some of the most important priorities to ensure UHC. Essential medicines are a focus of Sustainable Development Goal 3.8: “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all” [1]. The WHO Expert Committee defined that essential medicines “satisfy the health care needs of the majority of the population; [and] … therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford” [2].

Since its advent in 1977, the WHO Essential Medicines List (EML) has served as a model list globally. National EMLs (NEMLs) have been developed in over 137 countries [3]. While important gaps in accessing medicines remain, EMLs contribute in important ways to defining what medicines are reimbursed and ultimately available at the front lines of health care around the world [4]. Indeed, my first personal exposure to the EML was as a field doctor with Médicins Sans Frontières in the Democratic Republic of the Congo where the drug formulary was based on the EML and dictated what treatments we had available to use [5].

Since 1977 the WHO EML has expanded from 186 to 479 medicines. This increase reflects more licensed medicines to treat more conditions. In the 1970s when the EML was introduced, the average number of new molecular entities per year was 15; this has doubled to over 30 in the 2010s, accelerating even further in recent years with the advent of new medicine classes such as biologics [6]. This proliferation and the commensurate increase in the number of medicines listed on the EML has both increased the complexity of health care practice, and challenged the very concept of 'essential' for essential medicines [4].

In the evolution of NEMLs there has been substantial divergence from the WHO EML both in listing many more, or many less medicines nationally. Among the 137 known NEMLs, the number of medicines varies from 44 – far less than the WHOs 479 medicines – to more than double at 983 [7]. The diversion from the WHO EML is highest in the WHO European Region countries and lowest in South-East Asia Region Countries [7]. There is also high variability that cannot be readily explained by anatomic therapeutic class of medicines. Certain countries, including Canada, do not have a NEML despite support for this among decision-makers [8].

While the EML is a guiding document intended to improve availability of medicines and therefore universal health coverage, the availability of essential medicines in practice has been problematic and inconsistent [9]. Furthermore, the ability to assess availability of essential medicines through monitoring data needs improvements [4].

Criticisms of Essential Medicine List Decisions

Decisions by the Expert Committee for the WHO EML have been criticized on a number of fronts. These have included the composition and appointment of Expert Committee members and concerns regarding potential conflicts of interest [10]. Criticism on inconsistency in decisions particularly regarding the inclusion of higher cost medicines such as direct acting antivirals for hepatitis C, but not similarly costly cancer medicines [11]. It has also included criticism that the concept is impracticable or difficult to implement for high-income countries [12].

Finally, in 2014 Barbui and Purgato enumerated a number of concerns following a review of anti-depressant and anti-psychotic medicines and corresponding applications [13]:

1) Search strategy inconsistently reported, reasons for inclusion or exclusion of data not reported;

2) Target population, comparison groups, and outcomes of interest erratically reported;

3) Quantitative summaries of overall treatment effect not systematically reported for each comparison and outcome;

4) Quality of evidence erratically reported;

5) Considerations not related to the evidence base inconsistently reported;

6) Conflicts of interest not clearly reported;

7) WHO expert committee narratively reports reasons for accepting or rejecting a medicine.

The WHO EML has evolved to address these concerns since 2014, in particular improving transparency. The review reports on applications, as well as decision feedback are all published transparently on the WHO website [14]. Additionally, the recently developed essentialmeds.org website catalogues all medicines listed and applied in a systematic way [15]. However, questions on decision-making processes and included medicines remain.

Connection Between EMLs and Guidelines

Barbui and Purgato proposed that solutions to problems 3 and 4 above could include using methods advanced by the Guideline Recommendations, Assessment, Development and Evaluation (GRADE) Working Group [13]. A 2019 application to the EML for direct oral anticoagulants utilized GRADE evidence profiles and evidence-to-decision tables to present evidence derived from a systematic review and guideline, and was ultimately accepted by the Expert Committee [16].

Efforts to strengthen linkage between guidelines and EMLs, among other health decision frameworks has been recently reinvigorated [17]. This is a longstanding priority; a 2017 presentation to the Expert Committee by Secretariat Nicola Magrini referenced relationships with WHO guidelines as a key future approach for the EML [18]. Indeed, in the 2001 WHO Executive Board resolution on the revised procedure for updating the WHO's Model List of Essential Drugs (EB109/8), the linkage guidelines and the EML was referenced 14 times including statements such as the "Expert Committee stressed the importance of the link between selection of medicines for the Model List and clinical guidelines" [19]. The Lancet

Commission on Essential Medicine Policies also emphasized evidence-informed treatment guidelines as a key measure to improve prescribing, price and ultimately access to essential medicines [4].

While recognizing other critical aspects of access such as health system and financing mechanism, implementation, and quality improvement, we specifically are not addressing those aspects of access here to focus on the link between guidelines and EMLs. The linkage between guidelines and EMLs has intuitive logic. Guidelines set recommendations for or against and EMLs prioritize medicines. Thus, the most important medicines recommended by guidelines should be considered for EMLs, and essential medicines should have underlying guidelines recommending their use. Furthermore, alignment between the two processes could decrease the time lag between recommendation by a guideline and their ultimately reimbursement and availability. Finally, alignment of guidelines and EMLs could improve the quality of both health decision products and decrease evidence synthesis waste by scaling resources collaboratively. While the desire to bring guidelines and EMLs in closer alignment has been longstanding, no research work has to date explored opportunities to operationalize.

Goals and Scope

In this dissertation I explore the linkage and ways forward for synergy between guidelines and EMLs, with particular attention to the WHOs EML. I set out to accomplish this through three goals:

1. Identify key criteria and considerations for evidence synthesis with guideline and EML stakeholders.
2. Explore the experience of users, including applicants, technical advisors, and committee members, of an evidence-to-decision framework tailored to essential medicines and applications to EMLs.
3. Identify challenges, and potential solutions for trustworthy, evidence-based essential medicine lists from the perspective of content, technical and methodological experts, through GRADE guidance.

Through these goals, the overall scope of the thesis is to identify and test strategies to bring EMLs and guidelines in closer alignment.

Thesis Overview

In chapter 2 I answer the question "What is the EML decision process?", to explore connections to established guideline decision processes. In chapter 3, I build on this to develop an evidence-to-decision framework tailored to the EML decision process and test this with EML applicants, technical experts and expert committee members. In chapter 4, I use established methods for advancement of methodological consensus in the GRADE Working Group to develop GRADE guidance informing Essential Medicine Lists. The overarching objective of this thesis is to explore and advance synergy between guidelines and EMLs to support the development of trustworthy EMLs and ultimately improve access to essential medicines within the critically

important global priority of access to UHC. Finally in chapter 5, I review key conclusions and future policy and research directions for the connection between EMLs and guidelines.

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Chapter 2: Decision Criteria for Selecting Essential Medicines and their Connection to Guidelines: An Interpretive Descriptive Qualitative Interview Study

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Abstract

Objective:

The World Health Organization Model List of Essential Medicines has led to at least 137 national lists. Essential medicines should be grounded in evidence-based guideline recommendations and explicit decision criteria. Essential medicines should be available, accessible, affordable, and the supporting evidence should be accompanied by a rating of the certainty one can place in it. Our objectives were to identify criteria and considerations that should be addressed in moving from a guideline recommendation regarding a medicine to the decision of whether to add, maintain, or remove a medicine from an essential medicines list. We also seek to explore opportunities to improve organizational processes to support evidence-based health decision-making more broadly.

Study Design and Setting:

We conducted a qualitative study with semi-structured interviews of key informant stakeholders in the development and use of guidelines and essential medicine lists (EMLs). We used an interpretive descriptive analysis approach and thematic analysis of interview transcripts in NVIVO v12.

Results:

We interviewed 16 key informants working at national and global levels across all WHO regions. We identified five themes: three descriptive/explanatory themes 1) EMLs and guidelines, the

same, but different; 2) EMLs can drive price reductions and improve affordability and access; 3) Time lag and disconnect between guidelines and EMLs; and two prescriptive themes 4) An ‘evidence pipeline’ could improve coordination between guidelines and EMLs; 5) Facilitating the link between the WHO Model List of Essential Medicines (WHO EML) and national EMLs could increase alignment.

Conclusions:

We found significant overlap and opportunities for alignment between guideline and essential medicine decision processes. This finding presents opportunities for guideline and EML developers to enhance strategies for collaboration. Future research should assess and evaluate these strategies in practice to support the shared goal of guidelines and EMLs: improvements in health.

Background

Recommendations about medicines by health guideline developers and decisions about essential medicine lists (EMLs) are both important instruments to support health decision-making. EMLs use a medicine-focused approach, while guidelines use a disease/problem focused approach. They both strive to improve individual and population health outcomes through better policy decisions and more appropriate prescribing [1]. On the one hand, if a medicine is considered “essential”, trustworthy practice guideline recommendations to guide its most appropriate use should also be available. On the other hand, medicines recommended by practice guidelines should be available, accessible, affordable, and of good quality, and at least be evaluated for “essential medicine” status.

Essential medicines are defined by WHO (2001 criteria) as medicines that: 1) meet the priority health care needs of the population, 2) are selected based on public health/disease prevalence, evidence of efficacy and safety, and comparative cost-effectiveness, and 3) are intended to be available at all times within functioning health systems in adequate amounts, dosage forms, and quality assurance at an affordable price [2]. Listing the medicine on the EML can improve access to medicines through prioritization for procurement, quality assurance, distribution, reimbursement and use. While essential medicines are more widely available globally than non-essential medicines, access to them is still inequitable [3].

The Model List of Essential Medicines, produced by the World Health Organization (WHO) since 1977, prioritizes medicines, identifying the most effective therapeutic options in each disease area. It serves as a global reference list and as a model list for national EMLs and reimbursement. The WHO EML is important because it supports Universal Health Coverage (UHC) for all, and the UN Sustainable Development Goal #3, which strives to develop “access to safe, effective, quality, and affordable essential medicines and vaccines for all” [4].

The Expert Committee on Selection and Use of Essential Medicines updates the WHO EML every two years. This multidisciplinary panel is composed of about 10-20 experts, which act in their own capacity, with expertise and experience in medicine assessment and policy. At least 137 countries produce and use national EMLs [2]. The implication of a national listing of a medicine is that governments should ensure that the included essential medicines are available, accessible, affordable, and of good quality at all times [2]. National lists are developed for context-specific application of the EML, which every country should ideally produce to support UHC. The WHO has recently produced an implementation guide to facilitate the evidence-based development of national EMLs [2].

Any individual or organization can apply to make an addition, deletions, or changes to the WHO EML. Decisions are made based on applications submitted and all submitted data and reviews made publicly available by WHO with opportunities for interested parties to comment. Each application describes the request for change and provides evidence and other elements supporting the request. Considerations that have traditionally gone into EML applications, presented in the WHO EML application are informed by the 2001 WHO Executive Board resolution. Not all criteria that the EML application requests are comprehensively presented in applications to the EML. Review of applications may identify important information, but EML committees may be missing important information for decision-making. For example, Moucheraud and colleagues found that only 6% of applications to the WHO EML expert committee between 2002 and 2013 contained complete pricing information [5]. There are criteria and evidence that have been omitted from applications, but there may also be medicines where that information is simply not available.

Growing, but longstanding interest in linking EML decisions to health guideline recommendations exist [1]. This involves strengthening the synergies between selection of therapeutic options, a phase associated with procurement and purchasing, and the actual use of

medicines at clinical level. Gray and colleagues highlight the question “should the list automatically include any medicine mentioned in a WHO treatment guideline?” [6].

Evidence-to-decision (EtD) frameworks facilitate guideline committees to support effective guidance that considers a wide range of important considerations [7-9]. They are currently being used by a wide-range of WHO and other guideline development groups. The use of EtD frameworks, or closer linking, in supporting EML applications could make criteria clearer and explicitly included. EtD frameworks support guideline groups to provide judgements on a series of criteria to bridge the evaluation of evidence to making a recommendation regarding an intervention. The GRADE system may be used to estimate and indicate the certainty of the supporting evidence. The typical questions considered in the standard EtD process are included in Box 1; however, GRADE EtD frameworks, when appropriate, allow tailoring of criteria and judgements.

Box 1. Questions/Decision-Criteria for WHO EML Applications and Guideline EtDs

Product	WHO EML Application Criteria [10]	Guideline EtD Criteria [7-9]
Decision criteria	• Public health relevance (item 8 of the standard application form). • Review of benefits: clinical evidence, summary of available data and summary of available estimates of comparative effectiveness (item 9). • Review of harms and toxicity: estimates of total patient exposures, description of adverse events and estimates of their frequency, summary of available data, summary of comparative safety against	• Is the problem a priority? • How substantial are the desirable and undesirable anticipated effects? • What is the overall certainty (quality) of the evidence of effects (following GRADE criteria)? • Is there important uncertainty about or variability in how much people value the main outcomes? • Does the balance between the desirable and undesirable effects favour the intervention or the comparison?

	comparators, identification of variation in safety that may relate to health systems and patient factors (item 10). • Summary of available data on comparative cost and cost-effectiveness of the medicine (item 11). • Summary of regulatory status and market availability of the medicine (item 12). • Availability of pharmacopoeial standards (item 13) (also referred to as prequalification and manufacturing standards).	• How large are the resource requirements (costs)? • What is the certainty (quality) of the evidence of resource requirements (costs)? • Does the cost effectiveness of the intervention favour the intervention or the comparison? • What would be the impact on health equities? • Is the intervention acceptable to key stakeholders? • Is the intervention feasible to implement?

Although the WHO EML selection criteria and EtD framework were conceived at different times, and in different contexts, the parallels are clear [1]. For example, both approaches consider desirable and undesirable health effects, comparative cost-effectiveness, and availability of appropriate medicines. Differences between EML considerations and EtD frameworks may have important implications. There are considerations discussed by EMLs that are only implicitly incorporated into the EtD framework, e.g. under acceptability and feasibility; these include, therapeutic equivalence (i.e. square box listing, which groups medicines with therapeutic equivalency [11]), patents, on/off label uses, procurement, purchasing and availability. There might be also differences in the nature of the evaluation process: guideline panels often start with the disease and often assess several clinical questions in relation to a single disease area, while the EML expert committee starts with the medicine and assesses a single question (is the medicine essential for a given indication?) across several diseases.

In addition to selection criteria considered, a robust process is also important for the development of trustworthy EMLs. One such process consideration is the selection of experts

for the Expert Committee, which are chosen every two years by WHO from a standing list of technical experts proposed by WHO and approved by WHO member states; and the careful management of their potential conflict of interest. The lack of management of potential conflict of interests in EMLs has previously been subject to criticism [12].

Improving EMLs and their synergy with guidelines requires a greater understanding of the current state of these decision paradigms and their interplay. Our objectives were to identify considerations that should be addressed in moving from a guideline recommendation regarding a medicine to the decision of whether to add, maintain, or remove a medicine from an EML. The opposite trajectory is also possible, with a medicine first listed as essential and then considered by guideline recommendation. To achieve these objectives, our research question was: what are the perspectives and experiences of experts from both EML and guideline contexts with decision-making criteria for essential medicines? In this article we specifically seek to describe the current processes and opportunities. We also seek to explore opportunities to improve organizational processes to support evidence-based health decision-making more broadly.

Methods

Research Protocol, Ethics Review and Consent

We developed a research protocol and report this work in accordance with the COnsolidated criteria for REporting Qualitative research (COREQ) checklist (available in appendix 1) [13]. The protocol was developed in coordination with the WHO Secretariat of the Expert Committee on the Selection and Use of Essential Medicines, to ensure strong integration of research results into global and national EML processes. The Hamilton Integrated Research Ethics Board (HIREB) approved this research (approval # 7534). We obtained written consent from all participants in accordance with institutional protocol.

Participant Recruitment

We began by identifying two preliminary lists of key informants drawing from two paradigmatic expertise groups: EML experts and guideline experts. The list was developed through expert input of study authors familiar with global EML and guideline experts and online searches (google search and google scholar search: “essential medicine list”). From this long list we categorized respondents as technical experts, methodologists, clinicians, patient advocates, and policy-makers. Additionally, we categorized by organization type, professional background, geography, gender, and racial backgrounds. Participants were recruited with attention to diversity across all of these domains to provide equitable and representative input. We used a respondent-driven sampling approach seeking additional participant referrals from all participants interviewed expanding the original list of possible experts, and continued recruitment until theoretical saturation was reached. We invited all preliminary key informants to participate using a defined e-mail script and consent form that was approved by HIREB. We followed up with key informants on at least two additional occasions, at least 2 weeks apart if they did not respond to our initial invitation. We balanced participant recruitment in the two expertise groups.

Development of Interview Guide and Background Briefing Documents for Participants

We reviewed key WHO documents, national EML technical documents and GRADE EtD publications to compile information on decision criteria and processes in EMLs and guidelines. We assessed EMLs and guideline EtD frameworks and developed an interview guide to inform key informant interviews. We generated two different background briefs for participants, tailored to their expertise and planned focus of the interview: EML or guideline oriented decision-making (available appendix 2) [2]. We sent this background brief to participants for their reading one

week or greater before the interview. The guideline background brief described guideline development processes, and decision-criteria across a range of guideline recommendation types (health system & public health, clinical, coverage decisions etc.) (available appendix 3) [7-9, 14, 15]. Both background briefs shared the same sample EML applications to inform the discussion.

Semi-Structured Qualitative Interviews

The semi-structured interview guide is available in appendix 4. An interviewer trained at the graduate level in qualitative interview (TP) conducted semi-structured open-ended qualitative interviews. Participants were asked to read the background brief shared with them in advance of the interview. The first interview was conducted to pilot the interview guide with a co-author (LM). We debriefed and refined the interview approach, keeping the semi-structured guide constant through the course of the interviews. We conducted debriefing sessions throughout the interview process with key collaborators (TP, HJS, LM, EAA, JL). All interviews were conducted via Zoom (Zoom Video Communications, California, USA) or Webex (Cisco Webex, California, USA) and video-recorded with written participant consent. Video recordings were transcribed by one investigator (TP) immediately following their completion and video recordings were retained for reference on respondent tone and context during the analysis period.

Reflexivity, Interpretive Descriptive Coding and Thematic Analysis

This research was led by researchers at the MacGRADE centre (TP, HJS) in collaboration with staff from WHO Access to Medicines and Health Products Division (LM, BH). The authors have methodological involvement in guidelines, including as members of the GRADE working group, or as members of essential medicine list committees. The authorship

group is primarily, but not entirely, from the global north. In keeping with reflexivity on personal privilege that may inform research perspectives, the lead researcher TP is a cis-gendered male, white, settler in Canada. We strive to be reflexive on position and perspective in the analysis presented.

Interviewer journaling to support reflexive analysis was conducted through each interview and reviewed with the authorship group at several stages through the interview recruitment process. One investigator (TP) uploaded the transcribed interviews into NVIVO v12 (QSR International, Melbourne, Australia). We kept an interviewing journal for reflective discussion through the progress of interviews. After the completion of 3 interviews from each expertise group, we began preliminary coding, using an coding methodology within NVIVO v12 [16]. We reviewed preliminary codes and preliminary themes as a research team at interim reviews, and team review was conducted to verify theoretical saturation and completion of participant enrolment (TP, HJS, LM, EA, JL). We used an interpretive descriptive inquiry methodology to explore our research question and develop our final thematic analysis for presentation [17].

Results

We identified 42 potential experts, invited 25 key informants and ultimately conducted 16 interviews (response rate 64%). Of the 9 individuals not participating, 3 declined due to time limitations and 6 did not respond after 3 attempts to contact. Characteristics of each participant are available in appendix 5 and summarized in table 1. The majority of participants were male (11, 69%) and working in the WHO European region (9, 56%). However, all WHO regions were represented among participants. Interviews were a median of 41:15 minutes in duration (range 26:20 to 61:22 minutes).

Table 1. Participant Characteristics.

Characteristic	Characteristic	Number	Percentage
Gender	Female	5	31%
	Male	11	69%
	Other/Not Reported	0	0%
Primary Expertise	EML	9	56%
	Guideline	7	44%
Perspective*	Academia	7	44%
	National EML Staff	5	31%
	National Guideline Staff	1	6%
	WHO Department	1	6%
	WHO Model List of Essential Medicine	5	31%
WHO Region of Work	AFRO	2	13%
	EMRO	1	6%
	EURO	9	56%
	PAHO	2	13%
	SEARO	1	6%
	WPRO	1	6%

*more than one response possible

We coded the 16 interviews using 64 preliminary codes at 252 locations. Codes were then classified into 7 labelled categories and an “other” category. The table of coding frequency is available in appendix 5. Most frequently the labelled codes related to cost-effectiveness, connection of guideline to EML, duplication of work, transparency of EML decisions, and WHO coordination.

Thematic analysis of coded quotes yielded five themes, themes 1-3 were descriptive and explained the current processes and challenges with guidelines and EMLs, while themes 4-5 were prescriptive in nature with recommendations to improve processes around EML and guidelines, and their connection. Box 1 shows the final themes identified through thematic analysis. Key quotes are presented by theme in appendix 6.

Box 2. Final Themes

1. EMLs and Guidelines, the same, but different;
2. EMLs can decrease price and improve affordability and access;
3. Time lag and disconnect between guidelines and EMLs;
4. An evidence pipeline could improve coordination between guidelines and EMLs;
5. Facilitating the link between the WHO EML and national EMLs could increase alignment;

Theme 1: EMLs and Guidelines, the same, but different

The first theme includes the similarities between the objectives and processes of guidelines and EMLs. In discussing the application process and questions for the WHO EML, respondents felt there was important overlap between the EML and guideline decision criteria and multiple respondents felt the two processes needed to be more effectively interlinked. While conceived for different purposes, guidelines to inform clinical practice and decision-making, and EMLs to support procurement, purchasing, and access to medicines, their decision criteria have many shared elements. Decision criteria that are shared between both guidelines and EMLs were problem priority/public health relevance, benefits, harms, and comparative cost-effectiveness.

Participants described that equity is considered as a key criterion in EtDs in guidelines, but not explicitly considered on an EML application. Medicine production and availability were considered by EMLs, but not often explicitly by guidelines. Availability of pharmacopeial standards is considered by EMLs, but not often by guidelines.

Criteria we found distinct to guideline decisions included values & preferences, equity, acceptability, and feasibility (which is implicitly considered in market availability) although decision makers integrate values implicitly when weighing desirable and undesirable effects. Criteria unique to EMLs included regulatory status and market availability, and pharmacopeial standards. Feasibility is intended to incorporate approved indications and access to the

medicine in the original GRADE EtD [8]. Figure 1 visualizes the use of guideline EtD and EML application criteria. Some respondents reflected that while explicit mention of other considerations are not listed in the application (for example health equity) they play an important role in the WHO's EML Expert Committee review assessment and are therefore important criteria. Additionally, while feasibility, which is an EtD criterion is not an explicit EML criterion, regulatory status, market availability and pharmacopoeial standards are factors impacting the feasibility of listing a medicine on an EML. Finally, the output differs, with the output of a guideline being the formulation of a recommendation (e.g., clinical or public health) and an EML committee ultimately making decisions around inclusion or removal of a medicine on the list.

Figure 1. Shared and distinct decision criteria for guideline EtDs and EML applications (from the WHO EML application criteria).

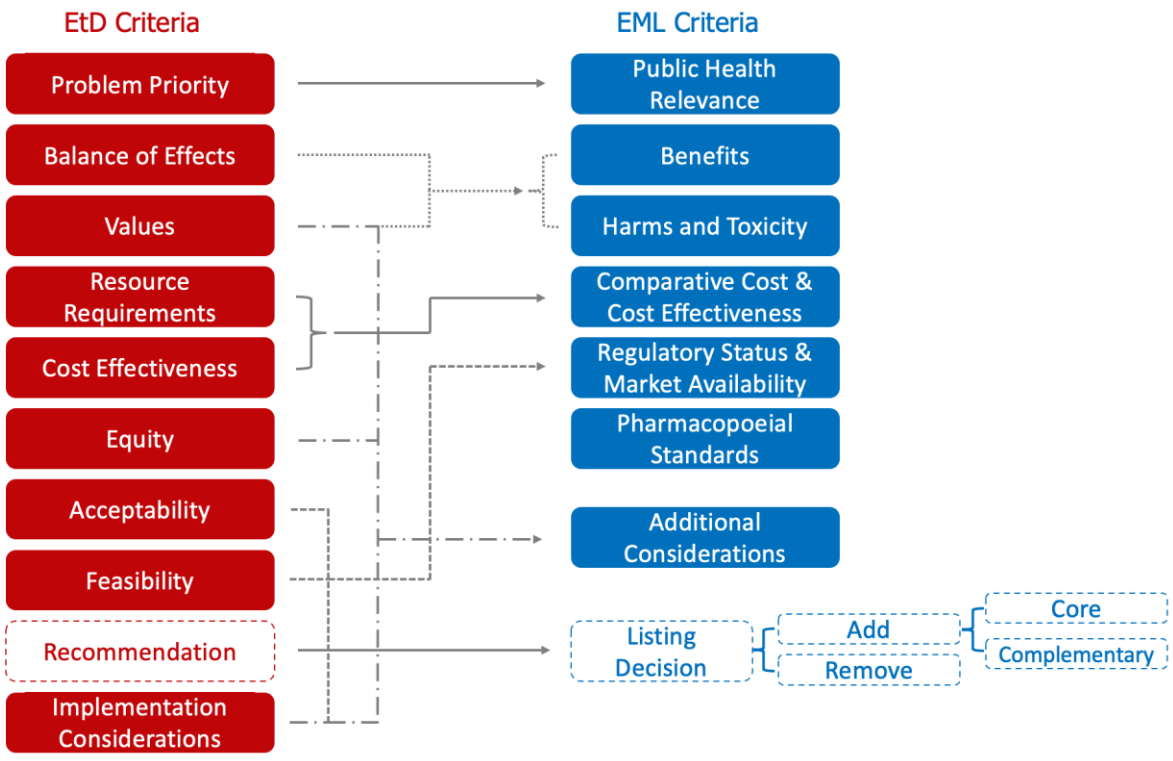

Figure description: this figure visualizes the decision criteria for guideline evidence-to-decision processes and EML applications. Solid lines draw connections between EtD criteria and EML criteria. Dashed lines highlight decision criteria, for a guideline this is a recommendation (strong

or conditional), for an EML this is a listing decision. Listing decisions can be to add or remove a medicine from the core or complementary EML.

Theme 2: EMLs can decrease price and improve affordability and access

The second theme we identified was the unique impact that EMLs can have in improving access and affordability of medicines through focusing the market on the purchasing of a select number of essential medicines. Respondents shared that this can decrease cost by increasing demand for select priority medicines, increasing purchasing volumes, and improving negotiation opportunities for bulk purchasing. This could have significant benefits decreasing price and improving health equity in access to medicines for important health conditions. One prominent example discussed was HIV. The efforts to focus on selecting priority antiretrovirals (ARVs) for HIV led to increased quality of prescribing and focused the market on the most essential medicines, which contributed to improved access and greatly decreased cost [18].

Theme 3: Time lag and disconnect between guidelines and EMLs

The third theme reflects a time lag and disconnect between the creation of guidelines and EMLs. This creates delays in the listing of medicines onto EMLs and may decrease access to essential medicines that guideline groups are recommending. Experts voiced that the two-year time cycle for review for the WHO EML can delay the listing of new medicines recommended by guidelines. This may also be true at a country-level depending on the frequency of national EML updates. For guideline groups who may review the evidence and issue recommendations, some participants suggested that they could be given authority to add medicines to an EML directly, or after verification by a separate EML review committee. There are instances we identified, including in South Africa, where guideline groups issue recommendations directly adding/removing medicines from the national Essential Medicine List

improving coordination, decreasing duplication of work, and decreasing time lag to listing medicines.

One respondent shared the 2002 WHO EML experience where the HIV guideline development group and the WHO Expert Committee on the Selection of Essential Medicines were intentionally collaborating and meeting in the same week in the same building. By the end of the week WHO's evidence-based clinical guidelines for HIV developed by the first group were fully reflected in the first list of ARVs included in the WHO EML by the Expert Committee. Both documents were published around the same time. This example was provided as an example of thoughtful coordination to decrease the time lag to listing of essential medicines.

Theme 4: An evidence pipeline could improve coordination between guidelines and EMLs;

In the fourth theme, respondents articulated specific challenges in coordinating between guidelines and EMLs. This applied to effective listing of medicines by the WHO EML, because of variable quality and frequency of applications by WHO departments and other guideline-producing bodies. Where no WHO department exists for a health condition (e.g., dermatology), respondents also reflected on gaps in WHO EML listings. One specific suggestion for improved coordination within WHO and national EMLs, included overlapping representation of individuals involved in guidelines and the EML.

Respondents also suggested that an “evidence pipeline” for evidence synthesis could improve efficiency and coordination of guidelines and EMLs. This concept would coordinate research synthesis efforts from primary research across multiple types of health decision efforts (e.g. systematic reviews, EMLs, guidelines, health technology assessments) [1]. This work to coordinate has been broadly presented previously, however, we have developed a more

specific visual conceptualization of a possible global evidence pipeline for coordination of guidelines and EMLs in Figure 3.

In discussing an evidence pipeline, respondents highlighted the significant redundancy in research synthesis, including systematic reviews for practice, a multitude of guidelines, essential medicine lists, health technology assessments and other purposes. If an evidence pipeline coordinated research synthesis, the same high-quality evidence should be used across a range of areas. One respondent reflected that an improved connection between the WHO EML and national EMLs could also support the linkage of an evidence pipeline globally because international and national evidence synthesis efforts are often duplicative and not aligned.

Figure 3. A possible evidence pipeline for guidelines and EMLs.

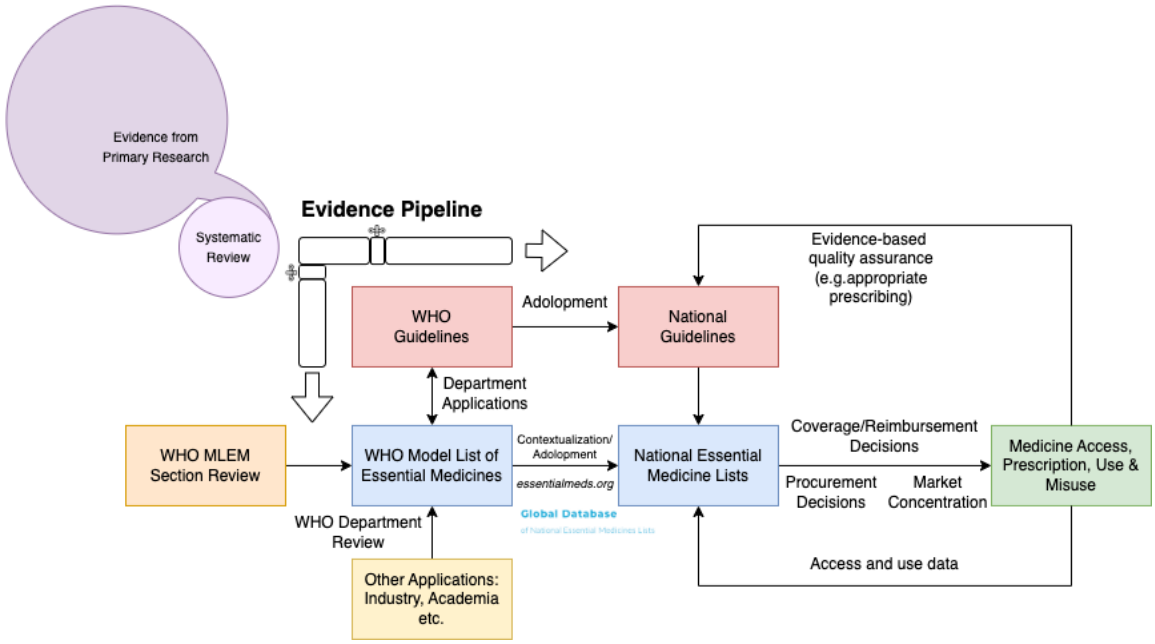

Figure description: Evidence from primary research is synthesized by systematic reviews. This common evidence base from systematic reviews feeds the evidence pipeline that could be applied to different purposes including guidelines at WHO or national level, and applications to the WHO EML or national EMLs. Listing at a national level ultimately impacts access, prescription, use and misuse of medicines. Adolopment – a GRADE term conceived as a contraction of adapt/adopt/de novo development refers to the EtD-based standardized process to contextualize guidance from one setting to another.

Theme 5: Facilitating the link between the WHO EML and national EMLs could increase alignment;

A fifth and final theme related to linking the WHO EML listings and process with national EMLs. Research has found wide variability in national EMLs including lists that are more restrictive and not nearly restrictive enough to be “essential” [19, 20]. One challenge repeatedly identified as driving the disconnect is capacity at the national EML level. However, even where there is capacity, sometimes there is still no comprehensive connection to the WHO EML and the evidence produced for those initial applications. This may result in duplication of work and represents an opportunity to better share evidence and decision-criteria to improve alignment and efficiency. Respondents suggested improving the quality and alignment between WHO EML and national EMLs through support for capacity in national EMLs and aligning application processes. Respondents suggested possibly creating a software solution for EML application and decisions that might support an online portal for information to be shared between stakeholders at global and national levels.

Discussion

In this qualitative research, we explored the processes and decision criteria informing both guidelines and selection of essential medicines. We identified important overlap in processes and the opportunity to better coordinate, both within WHO, and between other levels of health decision-making. We also identified shared and distinct decision-criteria, and an important role for both guidelines and EMLs, particularly at the WHO global level, in driving improvements in health outcomes and equitable access to essential medicines. In the current context, significant duplication of work and challenges with capacity may mean there are

conditions and countries that may not be as well served by evidence-based EMLs. Our interpretive descriptive qualitative methodology offers important new areas of study for the present practice and future development of guidelines, EMLs and their interface.

Strength and Limitations

Strengths of our study include the exploratory qualitative methodology in a nascent field of health evidence decision-making with an emphasis on guidelines and EMLs, which has so far been minimally explored. Another strength is the positioning of this exploratory research in the context of both guideline and EML decision paradigms. Starting from both guideline and EML decision orientations, we prepared background briefs that were tailored to each paradigm, and purposefully selected participants to inform this work from both paradigms.

Limitations of our study include reduced emphasis on national EMLs among our respondents and findings, as compared to the WHO EML. Our work was primarily driven by an examination of the WHO EML, and further work should explore differences at national levels by country and context. Additionally, the study is limited to qualitative interpretation of the case studies and historical example from interview respondents. Independent triangulation and validation of these examples is required in future research. Finally, additional work of specific applications and assessment of strategies is needed to bring alignment in decision processes between guidelines and EMLs.

Implications for practice and policy

We have identified opportunities to align decision-criteria and processes more closely between health guidelines and EMLs in practice. This includes improving coordination between WHO treatment guidelines and the WHO EML, creating an evidence pipeline to improve EML and guideline coordination and decrease duplication, and finally facilitating the link between the

WHO EML and national EMLs. This “evidence pipeline”, using similar EtD criteria to support EML applications, and contextualization tools for EMLs, warrants exploration to improve both the utility of guidelines and the impact of EMLs.

One opportunity for improving coordination between the WHO EML and national EMLs is the work that has been done for guideline adoption, adaptation and de novo development, e.g. GRADE adolopment [15, 21, 22]. This method, where EtD frameworks produced by one guideline group are considered and contextualized by another, could decrease duplication of work, while still supporting an important contextualization process for countries that are producing their own EML and strengthen WHO EML to national EML linkages.

This work is linked to recent work we have led on the broader ecosystem for health decision-making, demonstrating synergy in the criteria between various health decision-making paradigms including guidelines and Essential Medicine Lists [1]. Future work will assess the use of EtDs to support EML applications and describe applications of this approach to real guideline and EML scenarios.

Implications for research

Further research including evaluation of strategies identified here is needed to improve coordination of guidelines and EMLs. This research should focus on evaluation at different levels of health decision-making from local/national guidelines and EMLs to a global context; the WHO should play a key role in these next steps. Methods for how to facilitate an evidence pipeline, and strategies to develop this concept are also needed. Finally, research to trace health guideline development in relation to the connection to EMLs and to bring their recommendations more closely aligned is needed for the practical application of the concepts explored here. This should include the identification of gaps where strong guidelines do not exist

for important essential medicines or groups of medicines to inform guideline development and prioritization.

Conclusions

Despite different origins, guidelines and EMLs share many commonalities, including decision-criteria and processes. We have identified opportunities to better align guidelines and EMLs. Universal and equitable access to medicines that have been classified as “essential”, is a critical component of universal health coverage and improvements in health equity. Alignment of processes and evidence synthesis that inform guidelines and EMLs is important to improve transparency, efficiency, and evidence-based decision-making to unite towards their shared objective: improvements in health through universal access to evidence-based treatments.

Declaration of Interest

Thomas Piggott: Member of the GRADE Working Group.

Lorenzo Moja: Staff member of the Secretariat of the Expert Committee on the Selection and Use of Essential Medicines and an employee of the WHO, Geneva, Switzerland.

Elie A. Akl: Member of the GRADE Working Group.

John Lavis: Declared none.

Graham Cooke: was the chair of the 2019 and 2021 EML Expert Committee. He is supported in part by the Imperial NIHR Biomedical Research Centre.

Tamara Kredo: Member of the GRADE Working Group, Co-director of South African GRADE Network and member South African Essential Medicines List Committee.

Hans Hogerzeil: Was secretary of the WHO Expert Committee from 1999 to 2007 and Director of WHO's Essential Medicines Department from 2003 to 2011. He declares unrelated consultancy work for WHO, the Access to Medicine Index, Health Action International, and Management Sciences for Health.

Benedikt Huttner: Staff member of the Secretariat of the Expert Committee on the Selection and Use of Essential Medicines and an employee of the WHO, Geneva, Switzerland.

Pablo Alonso-Coello: Member of the GRADE Working Group, Director Barcelona GRADE Center.

Holger Schünemann: Member and co-chair of the GRADE Working Group, Director Cochrane Canada and McGRADE Centre.

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Chapter 2: Appendix 1: COREQ Checklist [13]

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	8
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	8
Occupation	3	What was their occupation at the time of the study?	9
Gender	4	Was the researcher male or female?	9
Experience and training	5	What experience or training did the researcher have?	8
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	8
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	8
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	8
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	9
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	9
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	8
Sample size	12	How many participants were in the study?	10
Non-participation	13	How many people refused to participate or dropped out? Reasons?	10
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	9
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	9
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	10
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	9
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	9
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	9
Field notes	20	Were field notes made during and/or after the inter view or focus group?	9
Duration	21	What was the duration of the inter views or focus group?	10
Data saturation	22	Was data saturation discussed?	9
Transcripts returned	23	Were transcripts returned to participants for comment and/or	9

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	9
Description of the coding tree	25	Did authors provide a description of the coding tree?	10-11
Derivation of themes	26	Were themes identified in advance or derived from the data?	9
Software	27	What software, if applicable, was used to manage the data?	9
Participant checking	28	Did participants provide feedback on the findings?	9
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	23-26
Data and findings consistent	30	Was there consistency between the data presented and the findings?	10-15
Clarity of major themes	31	Were major themes clearly presented in the findings?	10-15
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	10-15

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Group 1: Essential Medicine Lists

A Background on EML Decisions

Background

The Model List of Essential Medicines (MLEM), produced by the World Health Organization (WHO) since 1977, prioritizes medicines, identifying the most effective therapeutic options in each disease area. Essential medicines are defined as those that "satisfy the priority health care needs of the population" [1]. At a national level, the implication of listing a medicine on an essential medicine list is that governments should ensure that essential medicines are available at all times "in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and community can afford" [1, 2]. The number of medicines listed on the MLEM has increased from 220 in 1977 to 460 in 2019, with the list also expanding to include core and complementary sub-lists, dedicated respectively to primary and secondary care, and since 2007 a sub-list collecting all medicines recommended for children. All list modifications follow a multi-step review process before being ratified. Applications to include new medicines or modify any aspect of actual listing are peer reviewed and thereafter are debated during an Expert Committee meeting. The Committee proposes a series of recommendations to the WHO Director General, that finally approves the deliberations of the Committee. The current process for selection of essential medicines is governed by the WHO Executive Board Report from December 7th 2001 *WHO Medicine strategy: Revised procedure for updating WHO's Model List of Essential Drugs* [2].

Applications

The process is open, transparent and democratic. Anyone can propose to add, delete or modify the Model List by preparing an application that explains the reasons beyond the requested change. All documents, applications, peer reviews and Committee's recommendations are published in the WHO website. Applicants to the WHO's Model Essential Medicine List are invited to provide information on a number of dimensions to support the Executive Committees decision on an application. These are presented in Box 1.

Box 1. Considerations for the Selection of Essential Medicines

- Public health relevance (item 8 of the standard application form).
- Review of benefits: clinical evidence, summary of available data and summary of available estimates of comparative effectiveness (item 9).
- Review of harms and toxicity: estimates of total patient exposures, description of adverse events and estimates of their frequency, summary of available data, summary of comparative safety against comparators, identification of variation in safety that may relate to health systems and patient factors (item 10).
- Summary of available data on comparative cost and cost-effectiveness of the medicine (item 11).
- Summary of regulatory status and market availability of the medicine (item 12).
- Availability of pharmacopoeial standards (item 13).

Peer Review

In addition to the considerations requested from applicants, the Expert Committee also receives peer review reports to help with its decision-making. The criteria that are used in the peer review, address criteria similar to those requested in the application. The peer review criteria are presented in box 2.

Box 2. Peer Review Report Criteria – MLEM [3]

1. Does the application adequately address the issue of the public health need for the medicine?
2. Have all important studies/evidence of which you are aware been included in the application?
3. Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
4. Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?
5. Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).
6. Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?
7. Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)
8. Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?
9. Please comment briefly on issues regarding cost and affordability of this medicine.
10. Any additional comments?
11. Please frame the decisions and recommendations that the Expert Committee could make.

Decision-Making by the Expert Committee

The Expert Committee on Selection and Use of Essential Medicines updates the MLEM every two years (last meeting April 2019). This multidisciplinary panel is composed of about 20 experts, who act in their own capacity, with expertise and experience in medicine assessment. They receive and consider applications and reviews for the addition, removal, or formulation change of essential medicines to make final judgements on accepting or rejecting applications.

Key Questions/Considerations

To facilitate the discussion some future directions that have been identified include:

- **Cost of Medicines**: cost is explicitly not a criteria that the Expert Committee should consider, however, it should consider relative cost-effectiveness which includes cost as a component [2]. Cost and cost-effectiveness are considered within the same therapeutic class or when therapeutic equivalence is assumed. Is this appropriate? Are there other concepts such as affordability or budget impact that should be considered?
- **Link to Guidance**: There is a growing interest in linking EML decisions by the Expert Committee to World Health Organization guidelines, including sharing the best available evidence and a together with guideline producers share a "coordinated evidence base" [4]. How do we move incrementally to a more closely linked process of guidelines and EMLs?
- **National EMLs**: Over 137 countries produce their own national EMLs (NEMLs). The number of medicines they list ranges from 44 to 943 [5]. Improved coordination could facilitate connection of the MLEM to national EMLs, while still recognizing that a certain degree of contextualization may be required for NEMLs in relation to the MLEM (e.g. local epidemiological considerations). How do we improve coordination of the MLEM and NEMLs?

Sample Applications

1. Direct-Acting Oral Anticoagulants (Application 2019).
2. Transexamic Acid (Applications in 2009, 2011)
3. An example of a cancer drug application includes: Trastuzumab (Application in 2013)

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Group 2: Essential Medicine Lists

A Background on EML Decisions & GRADE EtDs

Background

The Model List of Essential Medicines (MLEM), produced by the World Health Organization (WHO) since 1977, prioritizes medicines, identifying the most effective therapeutic options in each disease area. Essential medicines are defined as those that "satisfy the priority health care needs of the population" [1]. At a national level, the implication of listing a medicine on an essential medicine list is that governments should ensure that essential medicines are available at all times "in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and community can afford" [1, 2]. The number of medicines listed on the MLEM has increased from 220 in 1977 to 460 in 2019, with the list also expanding to include core and complementary iterations and a pediatric list. Applications also undergo a peer review process. The current process for selection of essential medicines is governed by the WHO Executive Board Resolution from December 7th 2001 *WHO Medicine strategy: Revised procedure for updating WHO's Model List of Essential Drugs* [2].

While guidelines, and GRADE methodology to support their development, have been conceived in different processes, much overlap exists in the consideration of medicine recommendations. In certain contexts and settings effective connection links guideline medicine recommendations to EML recommendations, however, in other settings the connection is less clear. We will now explore EML decisions and GRADE Evidence-to-Decision (EtD) frameworks to better identify overlap and opportunities - Better understanding how they complement one each other.

EML Applications and Decisions

Applicants to the WHO's Model Essential Medicine List are asked a number of questions to support the Executive Committees decision on an application. These are presented in Box 1. Applications then undergo peer review using similar criteria to those provided in the application to support the Executive Committees deliberations. During Executive Committee decision

Box 1. Application Criteria for the Selection of Essential Medicines

- Public health relevance (item 8 of the standard application form).
- Review of benefits: clinical evidence, summary of available data and summary of available estimates of comparative effectiveness (item 9).
- Review of harms and toxicity: estimates of total patient exposures, description of adverse events and estimates of their frequency, summary of available data, summary of comparative safety against comparators, identification of variation in safety that may relate to health systems and patient factors (item 10).
- Summary of available data on comparative cost and cost-effectiveness of the medicine (item 11).
- Summary of regulatory status and market availability of the medicine (item 12).
- Availability of pharmacopoeial standards (item 13).

GRADE EtD

GRADE Evidence-to-Decision frameworks (EtDs) evolved for guideline development and are endorsed by the World Health Organization for WHO guidelines. EtDs have many similar considerations to those used to judge applications to the Essential Medicine List. In table 1 we present EtD criteria from the clinical, coverage decision, and health system and public health EtD papers with details on segments that are relevant to the selection of essential medicines.

Table 1. GRADE EtD Criteria Relevant to the Selection of Essential Medicines.

EtD Criteria	*Detailed Judgement*	*Reference*
Problem	EtD Paper: Are the consequences of the problem serious (severe or important in terms of the potential benefits or savings)? Is the problem urgent? (Not relevant for coverage decisions) Is it a recognised priority (such as based on a political or policy decision)?	[3]
	Clinical: Disabling or fatal conditions are often of higher priority. A topic may be less important to the general population but very important to those affected.	[4]
	Coverage decisions: More major illnesses and more common problems may be more likely to be covered, though policies may differ (e.g. certain organizations may prioritize rare diseases for coverage). Where a problem is costly, a strategy that may save costs may be prioritized by people making coverage decisions.	[5]
	Health system and public health: Problem importance should be judged based on severity of problem, urgency and consequences, and whether it is a political priority.	[6]
Desirable Effects	EtD Paper: Judgements for each outcome for which there is a desirable effect.	[3]
Undesirable Effects	EtD Paper: Judgements for each outcome for which there is an undesirable effect.	[3]
Overall Certainty	EtD Paper: See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects.	[3]
	Clinical: The less certain the evidence, the less likely a strong recommendation is appropriate.	[4]
	Coverage decisions: A panel may postpone making a coverage decision if there is important uncertainty. Where evidence is promising but there is important uncertainty, coverage may be considered in the context of research. Certainty of evidence should be based on what people will value as important, though other considerations including population health considerations (e.g. antimicrobial resistance) may also be important to people making coverage decisions.	[5]
	Health system and public health: Decisions in public health and health systems shouldn't be impeded by low or very low certainty evidence, however, this will decrease likelihood that a panel will make a strong recommendation.	[6]

Uncertainty/Variability in Value of Main Outcomes	EtD Paper: Is there important uncertainty or variability in how people value each of the main outcomes?	[3]
	Clinical: Uncertainty or variability in how people value main outcomes may be a reason for a weak recommendation.	[4]
	Coverage decisions: As in clinical recommendations, coverage decision recommendations should depend on how people that are affected value the main outcomes. Variability in values should not necessarily impact coverage decisions, if there is a sufficient group who value the outcomes coverage may be warranted.	[5]
	Health system and public health: How much people affected value the important outcomes, particularly is the balance between benefits and harms is close, is very important.	[6]
Balance	EtD Paper: Judgements combined for Desirable, Undesirable, Certainty and Values to generate balance.	[3]
	Clinical: The greater the cost, the less likely an intervention should be recommended.	[4]
	Coverage decisions: Economic evaluations and budget impact analyses will be important (and are often required) for coverage decisions, as value for money should underly the decision to cover a particular medicine. The resources required for a coverage decision will be influenced by the number of people with a condition that may benefit from medication coverage.	[5]
Resource Requirements	EtD Paper: How large is the difference in each item of resource use for which fewer/more resources are required?	[3]
	Health system and public health: Due to limited resources, panels should consider not only the cost-effectiveness and budget impact of an intervention, but also alternative interventions. For health system and public health interventions, total costs (including training, implementation, monitoring etc.) should be considered.	[6]
Certainty of Resource Requirements	EtD Paper: Have all-important items of resource use that may differ between the options being considered been identified? How certain is the evidence according to GRADE guidance? How certain is the evidence of differences in resource use between the options? Is there important variability in the cost of items of resource use that differ between the options being considered?	[3]
Cost Effectiveness	EtD Paper: Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? Multivariable sensitivity analyses? Is the economic evaluation on which the cost effectiveness is based reliable? Is it applicable to the setting of interest?	[3]
Health Equity	EtD Paper: Are there groups or settings that might be disadvantaged in relation to the problem or interventions? Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention (option) for disadvantaged groups or settings? Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the intervention or the importance of the problem for disadvantaged groups or settings?	[3]

	Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?	
	Coverage decisions: Deciding to cover a medication can increase equity because those who can't afford a medication otherwise will have access.	[5]
	Health system and public health: Because a population perspective is taken, the impacts on disadvantaged groups should be considered. Given a population perspective, who will bear the costs or benefit from the savings, and how this will impact equity should also be considered.	[6]
Acceptability	EtD Paper: Are there key stakeholders who would not accept the distribution of the benefits, harms and costs? Are there key stakeholders who would not accept the costs or undesirable effects in the short term for desirable effects (benefits) in the future? Are there key stakeholders who would not agree with the importance (value) attached to the desirable or undesirable effects (because of how they might be affected personally or because of their perceptions of the relative importance of the effects for others)? Would the intervention adversely affect people's autonomy? Are there key stakeholders who would disapprove of the intervention morally, for reasons other than its effects of people's autonomy (such as in regard to ethical principles such as no maleficence, beneficence, or justice)?	[3]
	Coverage decisions: Acceptability of a coverage decision will be based on the benefits, harms, costs, and ethical considerations. Acceptability may vary among those who will be covered, those who won't be covered/affected (but may share in the cost), health providers, policy-makers and other key stakeholders.	[5]
	Health system and public health: The acceptability of the intervention should be considered across key stakeholders in health systems and public health, including "those affected, public officials and politicians, healthcare managers, the general public, healthcare workers and their unions, and special interest groups".	[2]
Feasibility	EtD Paper: *For decisions other than coverage decisions*: Is the intervention or option sustainable? Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it? *For coverage decisions*: Is coverage of the intervention sustainable? Is it feasible to ensure appropriate use for approved indications? Is inappropriate use (indications that are not approved) an important consideration? Is access to the intervention an important concern? Are there important legal or bureaucratic or legal constraints that make it difficult or impossible to cover the intervention?	[3]
	Coverage decisions: The feasibility will be influenced by the resources required, which is a function of the unit cost and number of people with a condition that may benefit from medication coverage. Feasibility will also be based on capacity to meet increased demand through coverage. Data needs to monitor appropriate and inappropriate use of covered treatments may also be an important consideration.	[5]
	Health system and public health:	[2]

	Recommended interventions should be feasible, and strategies to address barriers to their implementation should be considered.

Key Questions/Considerations

To facilitate the discussion some future directions that have been identified include:

- **Cost of Medicines**: cost is explicitly not a criteria that the Expert Committee should consider, however, it should consider relative cost-effectiveness which includes cost as a component [2]. Cost and cost-effectiveness are considered within the same therapeutic class or when therapeutic equivalence is assumed. Is this appropriate? Are there other concepts such as affordability or budget impact that should be considered?
- **Link to Guidance**: There is a growing interest in linking EML decisions by the Expert Committee to World Health Organization guidelines, including sharing the best available evidence and a together with guideline producers share a "coordinated evidence base" [4]. How do we move incrementally to a more closely linked process of guidelines and EMLs?
- **National EMLs**: Over 137 countries produce their own national EMLs (NEMLs). The number of medicines they list ranges from 44 to 943 [5]. Improved coordination could facilitate connection of the MLEM to national EMLs, while still recognizing that a certain degree of contextualization may be required for NEMLs in relation to the MLEM (e.g. local epidemiological considerations). How do we improve coordination of the MLEM and NEMLs?

Sample EML Applications

1. Direct-Acting Oral Anticoagulants (Application 2019) – this application was prepared using a GRADE EtD.
2. Transexamic Acid (Applications in 2009, 2011)
3. An example of a cancer drug application includes: Trastuzumab (Application in 2013)

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Development of an Evidence-to-Decision making Framework to Support Selection of Essential Medicines

Interview Guide

A. Participant Information

Participant no.:	
Participant name and contact information:	Name: Email/Telephone:
Location:	
Date:	
Interviewer/Note-taker:	
Recorder interview no.:	

B. Interviewer Checklist

For in person interviews:

- Confirm the date, time and location of the meeting. Send a reminder to the participant before the meeting.
- Printed copy of Interview Guide. Take notes (point-form preferred) in the spaces provided.
- Printed copy of draft list of items generated.
- Additional paper to take notes if needed.
- Audio recorder. Test the recorder before each interview.

For interviews by telephone or online Webex:

- Make sure you have the land line phone number or have set up the Webex
- For interviews by Webex, share the meeting link with the interviewee in advance; send the PDF of the draft list of items generated.
- Confirm the date and time of the call. Send a reminder to the participant before the meeting.
- Interview Guide form to take notes. Additional paper to take notes if needed.
- Audio recorder. Test the recorder before each interview.

C. Introduction and Consent Statement

Say: Thank you very much for agreeing to participate in this interview. We are asking colleagues and other people who have been involved in the development or use of essential medicine lists their views on the current process and the potential use of a framework to assist with making medicine recommendations.

We will use your input to draft an evidence-to-decision framework that we hope to pilot to help support decision-making by for essential medicine lists. Our hope is that this can support the development of more rigorous and trustworthy essential medicine lists.

Participant Consent Statement:

Say: The research study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). With your permission, the session will be recorded on tape for transcription and erased after the transcription has occurred. Transcribed data will be analyzed and coded into themes, and destroyed at the end of the study period and publication. De-identified coded themes will be destroyed after a period of 5 years. You may also withdraw your responses from the interview at any time.
Do you agree for the data collected in the study to be used anonymously in publication?

☐ Yes ☐ No Notes:

Do you also agree to have the interview recorded?

☐ Yes ☐ No Notes:

Ask: Do you have any questions before we proceed?

D. Questions

1. Before we begin I would like to just clarify your **current position** and **any involvement** or exposure you have had to **essential medicine lists**?
   Prompt: What about the WHO MLEM?

2. Given your knowledge and experiences with essential medicine lists, could you please begin by **describing how decisions** regarding the addition, maintenance, or removal of medicines from an essential medicine lists (MEML or National EML) are made?

Prompt: how are applications developed and submitted? What factors does the committee consider in judging EML applications?

3. Of the considerations you listed, which are <u>core</u> to the decision and which are <u>supplemental</u>?
   Prompt: interviewer will reiterate the considerations the candidate mentioned in question 1.

4. Background on EtDs: for decisions in health, to facilitate coverage decisions and to make recommendations and inform health systems choices more transparent a series of questions have been validated by the GRADE working group in a framework called EtDs. This work was done in collaborations with many partners, including the WHO.

   The questions considered in the standard EtD process include [2-4] – please review at the document we sent to you before the document.

   Among the existing EtD criteria (**<u>see cheat sheet sent previously</u>**), which would you judge are necessary, helpful, and not relevant to inform the selection of essential medicines?

5. Are there any additional criteria that you think are relevant for decisions about essential medicines [interviewer will share screen presenting various EtD frameworks: interventions, public health decisions, coverage decisions, diagnostic tests].

6. Given the large number of applications for essential medicine lists committees may have to make, which criteria do you think could be ommited for decisions about essential medicine list committees.
   Prompt: Are there considerations that should be added? Are there considerations that could be ommited? Would you agree with a modifiable approach that could be used differently depending on the nature of the application?

7. When, how, and by whom would you envision that EtDs could used in the development of essential medicine lists?
   Prompt: by applicants, by the selection committees, to inform policy-makers, to inform patients

8. What training or additional considerations will be required for essential medicine list committees to effectively use an EtD framework?

9. What unique considerations would be required if national EML committees were assessing an EtD created in an application for an EML? How could they make use of an EtD on a medicine completed for the WHO Model EML? What are the barriers/facilitators for the use of MEML EtDs for a national EML?

10. What unique considerations would be required for the WHO's model EML to use an EtDs completed in the development of national EMLs? What are the barriers/facilitators for the use of national EML by the MEML?

F. End of Interview

Say: Thank you very much for your participation and feedback.

Chapter 2: Appendix 5: Code Frequency Table, Organized by Theme and Alphabetically

Name	Frequency
1) EMLs and Guidelines, the same, but different	
Benefits and harms	1
Case studies	4
Children's essential medicine list	1
Comparing guideline to EML decisions	3
Connection of Guideline to EML	6
Consensus-based decision making	3
Differences between guidelines and EMLs	2
EML logistics	4
EML outcomes and judgements	1
EML prioritization	4
EML size	1
EMLs as a type of health guideline	1
Experience over evidence on committee	1
Feasibility	2
Key factors for decision-making	4
Pharmacopeial standards	3
Politics of EML decisions	2
Process of EML applications	1
Regulatory approval	1
Removing or delisting medicines from EML	2
Square box therapeutic equivalence	1
Strong recommendation	1
Transparency of WHO EML decisions	6
2) EMLs can decrease price and improve affordability and access;	
Affordability	4
Cost effectiveness	8
Drug availability	5
Emerging diseases	1
EML application process	4
EML committee membership	2
EML criteria considerations in Guidelines	3
Equity	2
Gaps on WHO EML	3
Length of EML	2
Market focus/concentration and price decrease	3
Universal health coverage	2

3) Time lag and disconnect between guidelines and EMLs;	
Delays in listing medicines on EML	1
Fast tracking medicines	1
Out of date recommendations	1
Section Review	4
Timing of WHO EML meetings	5
Working groups of WHO EML	1
4) An evidence pipeline could improve coordination between guidelines and EMLs;	
Duplication of work	6
Evidence pipeline	5
Investment in EMLs	1
Lack of Evidence in EML Applications	3
Pharmaceutical companies	1
Searching for existing systematic reviews to decrease duplication of work	1
Systematic reviews	3
People serving both EML and guideline groups	2
WHO Department Applications	5
5) Facilitating the link between the WHO EML and national EMLs could increase alignment;	
Adaptation of EMLs	1
Impact of EML decisions	3
Implementation	1
Low Income Countries	3
WHO EML Portal Website	2
WHO EML to National EML connection	3
National EMLs	5
National formularies	3
Software solution	2
State-level essential medicine lists	1

Chapter 2: Appendix 6: Key Quotes Organized by Theme

Theme 1: EMLs and Guidelines, the same, but different

- *"The EML committees are guideline committees." [Respondent 1].*
- *"I have had people tell me that the essential medicines list, it's the same as a guideline because you're making a recommendation, and I'm like, you know, you are making a recommendation obviously, though, to add or not add. But to me it's… it's hard for me to articulate that… But for me, it is a, you know, a different process because it's so focused on the drug, it for being in multiple conditions and settings." [Respondent 6].*
- *"I think probably, you may, I think you can replace entirely the duplication of the EML application with guideline EtDs" [Respondent 16].*
- *"It's almost a bit like a circle because if a medicine isn't recommended by a guideline, should it be an essential medicine? I don't know, but if there isn't guidance on how to use it, should it be on the list as well?" [Respondent 10]*
- *"Equity if you will, or fairness and that sense right? I don't see that on this list [in the WHO EML application], is that something that the expert committee discusses and if so, is it more informal rather than formal with that?" [Respondent 10]*
- *"Given the global scope of the WHO. Maybe some consideration of how this will impact on equity may be interest into put as well in the application, which is not captured in the EML application." [Respondent 16]*
- *"we have the famous case – infamous in my mind – where we listed a medicine that actually no one made because, uh, this was dispersible zinc. So this was for the children's essential medicine list. There was one manufacturer who was making dispersible zinc, and we listed it on the essential medicines list due to its benefit for diarrhea in combination with oral rehydration therapy. And we wanted that form. And we're trying to promote this dispersible form and pretty much as soon as we listed it, the one company making it stopped making it. So we had a drug on the essential medicines list that nobody made. Luckily, somebody started making it again." [Respondent 6]*
- *"Because if you give this strong recommendation for medication A but it's not available, then it's a problem. So the EML could be or way to ensure that this recommendation is implementable." [Respondent 5]*
- *"Pharmacoepial Standards, is that feasibility, or perhaps an implementation consideration?" [Respondent 4]*

Theme 2: EMLs can decrease price and improve affordability and access

- *"That's why until 1999 ARVs [for HIV treatment] were not on the essential medicine list because they were too expensive. It is madness to put something on the list, which is so expensive that nobody can afford because it makes the list useless. And then we bas ically changed after said no, no, no, no. If it is a huge public health priority and the drug is basically effective and also cost effective within its category, then it shoul d become affordable. So, you select the drugs on medical impact of public health and all these things, not affordability. That can follow if the medicine is named as essential. EML drug listing can drive price down." [Respondent 3]*
- *"In 2002 when, with the first [WHO EML] selection of ARVs [for HIV], at that time, there were about 30 ARVs on the market, for the EML we chose 12 and they were very cleverly chosen. I mean, the first-line and second-line, one for people who had TB, one in pregnancy. One was also a second-line for another [population]. I mean, it was a careful building where drugs also had different purposes, depending on the patient. Three years later, 85% of all medications available were these 12. It basically knocked out the other 18 and drove prices down." [Respondent 3]*

Theme 3: Time lag and disconnect between guidelines and EMLs

- *"They don't speak to each other. So, the treatment guidelines are developed. Some of them [EML medicines] are outdated so, the revision timelines for the treatment guidance and the EML, it's not synchronized." [Respondent 10]*
- *"because if they have just, let's say, renewed the list. Right? And the evidence comes a few months later and you have to wait two years on this, you know, until that that list can be renewed." [Respondent 2]*
- *"If you have a strong candidate [for the EML], that should be considered so, and I think maybe some way of fast-tracking process exception […] I wouldn't say that it should happen for everything, but maybe for drugs that are exceptionally well positioned." [Respondent 2]*

Theme 4: An evidence pipeline, Improving internal coordination between guidelines and EMLs;

- *"we just we just couldn't act on the [WHO EML] application [from a guideline group] because it was so poor, um and there was a lot of great information that went into the guideline. But, you know, we didn't have it. It wasn't sent to the committee in the right place, so yeah, so that was a huge issue." [Respondent 6]*

- *"I mean there are famous areas on the list, which are not covered basically because there's no WHO department. I mean, dermatology, being one, you know" [Respondent 3]*
- *"There should be some coordination [at WHO HQ] between the essential medicines and the guidelines produced. I guess it would require some someone to coordinate. People within the EML group, knowing that they're now considering whatever pediatric anti-retrovirals and making sure that the HIV program are aware of what's being considered" [Respondent 1]*
- *"Maybe these questions could be addressed by some key members of the EML committee who could also serve on our guideline, or at least if they were observers […] so you could have some people as kind of the go between the two processes. So both EML and guidelines have better information from the other and the two processes will be more closely aligned." [Respondent 2]*
- *"Yeah, I think if there was one pipeline for all the information, that would be great. So, you know, if there was one pipeline for the systematic reviews, the summary of findings tables. I mean, basically that and you have cases where this isn't the case because of timing, you know, the same reviews, uh, should be, you know, considered by the guideline committee and the Essential Medicines Committee." [Respondent 6]*
- *"it's just like with a guideline adaptation. We don't want every country to have to, you know, go creating their own guideline. I'm sure that, you know, I think essential medicine list adaptations are the same issue. That's important, too. How we can make that more efficient and cheaper for countries" [Respondent 6]*

Theme 5: Facilitating the link between the WHO EML and national EMLs

- *"But some countries have 1000 medicines. And if you have that many, it's not really discriminatory. It doesn't really help to focus where you spend money to* get *value." [Respondent 12]*
- *"Most countries use the WHO list. That's what they have. And then only a few countries actually have a process for, um, kind of making decisions that are there in their own ministry. They're such limited resource wise for people. Yeah, the capacity just isn't there." [Respondent 1]*
- *"So often the World Health Organization will consider a medicine for their model list, and then maybe a country will consider it because it was added to the WHO list. Or maybe they'll consider it independently because they think it's important. Um, but, you know, for each of these applications and reviews, there's information generated. Sometimes*

they're systematic reviews or other evidence. I'm just wondering if you think there's a better way that some of this could be shared and there could be some collaboration." [Respondent 7]

Chapter 3: User-Experience Testing of an Evidence-to-Decision Making Framework for Selecting of Essential Medicines

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Abstract:

Background

Essential medicine lists (EMLs) are important medicine prioritization tools used by the World Health Organization (WHO) EML and over 130 countries. The criteria used by WHO's Expert Committee on the Selection and Use of Essential Medicines has parallels to the GRADE Evidence-to-Decision (EtD) frameworks. In this study, we explored the EtD frameworks and a visual abstract as adjunctive tools to strengthen the integrate evidence and improve the transparency of decisions of EML applications.

Materials and Methods

We conducted user-experience testing interviews of key EML stakeholders using Morville's honeycomb model. Interviews explored multifaceted dimensions (e.g., usability) on two EML applications for the 2021 WHO EML – long-acting insulin analogues for diabetes and immune checkpoint inhibitors for lung cancer. Using a pre-determined coding framework and thematic analysis we iteratively improved both the EtD framework and the visual abstract.

Results

We coded the transcripts of 17 interviews in 103 instances across all dimensions of the user-experience honeycomb. Respondents felt the EtD framework and visual abstract presented complementary useful and findable adjuncts to the traditional EML application. They felt this would increase transparency and efficiency in evidence assessed by EML committees. As EtD frameworks are also used in health practice guidelines, including those by the WHO, the adoption of the EtD by EML applications represents a tangible mechanism to align EMLs and guidelines, decrease duplication of work and improve coordination. Improvements were made to clarify instructions for the EtD and visual abstract, and to refine the design and content included. 'Availability' was added as an additional criterion for EML applications to highlight this criterion in alignment with WHO EML criteria.

Discussion

EtD frameworks and visual abstracts present additional important tools to communicate evidence and support decision-criteria in EML applications, which have global health impact. Access to essential medicines is important for achieving universal health coverage, and their development should be as evidence-based and trustworthy as possible.

Background

Essential Medicine Lists (EMLs) are important for the prioritization and availability of medicines around the world. Essential medicine lists are a key prioritization tool to inform coverage decisions and steward limited health resources under the context of Universal Health Care (1). The World Health Organization (WHO) Model List of Essential Medicines (MLEM) has prioritized medicines since 1977 (2). Over 130 countries develop and use national essential medicine lists for their own context (3).

For a medicine to be deemed essential, the selection should be grounded in evidence of improved net desirable people-important health outcomes. Other dimensions than health outcomes should also be included in the evaluation process of the merits of medicines. In previous work, we found that EML committees and health practice guidelines utilize similar decision-making criteria (e.g. both consider criteria such as benefits and harms, cost and cost-effectiveness of medicines) (4). In the context of WHO, we identified variability among health guideline topics, and opportunities to standardize the flow of medicines recommended by WHO guidelines to consideration as an essential medicine by the WHO MLEM Expert Committee. The WHO Guideline Development Handbook recommends GRADE methods to inform guideline development processes, including using Evidence-to-Decision Frameworks (EtD) (5). These EtDs employ similar criteria to what has traditionally been requested in applications to WHO's EML (6).

A closer link will help both EMLs and health practice guidelines to better achieve their goals of supporting evidence-based decision making (4). Improved connection between guideline recommendations and EMLs involves synchronizing the processes used in both areas. Indeed, such coordination has sporadically been established between different WHO guideline-producing departments and the EML. In 2000, a simultaneously organized guideline and EML

meeting led to a direct connection between HIV treatment guideline recommendations and essential medicine listings (4, 7). Many WHO departments producing guidelines have mechanisms in place to assure that medicines recommended in guidelines are also assessed by the EML Expert Committee. We utilized the GRADE EtD criteria from a health guideline to support the request for addition of direct-oral anticoagulants in a WHO EML application, which was found to be a useful format (8). A forthcoming guideline from the MSIF was conceived to directly support application to the WHO EML (9).

This work fits within the context of broader work to coordinate decision criteria and processes between different paradigms in the ecosystem of health decision-making; EMLs and guidelines are two such paradigms (10). In the present qualitative study, we conducted user-experience testing of a proposed EtD framework for EMLs with key stakeholders engaged in EMLs including applicants, technical staff and committee decision-makers.

Methods

Overview

We used the honeycomb model for user-experience presented by Morville (11). User-experience testing presents a product for key stakeholders and observes usability, and asks directed questions about key characteristics of usability to inform improvements (11). The honeycomb model has been previously utilized in health sciences and evidence synthesis to test usability of products (12, 13). The dimensions centre around value of the product, with other dimensions including useful, usable, findable, credible, accessible, and desirable (11). We conducted user-experience testing interviews of key EML stakeholders to: i) explore the perceptions about an EtD framework and visual abstract as adjunctive tools to strengthen the integration of evidence and improve the transparency of decisions regarding EML applications;

and ii) ascertain how EtDs tailored to EML criteria could influence the coordination of guidelines and EMLs and influence the decision-making experience as perceived by key stakeholders.

Research Protocol, Ethics Review and Consent

We developed a research protocol in coordination with the WHO Secretariat of the Expert Committee on the Selection and Use of Essential Medicines, to ensure strong integration of research results into global and national EML processes. The Hamilton Integrated Research Ethics Board approved this research (approval #7534). We obtained written consent from all respondents in accordance with institutional protocol (see appendix 1).

Reflexivity

This research was led by researchers at the McGRADE and Michael G. DeGroote Cochrane Canada Centres and WHO Collaborating Centre for Infectious Diseases, Research Methods and Recommendations (TP, HJS) in collaboration with staff from WHO Access to Medicines and Health Products Division (LM, BH), and other experts. Authors have methodological involvement in guidelines, including as members of the GRADE working group developing the GRADE EtDs, and/or as members of essential medicine list committees. The authorship group is primarily, but not entirely, from the global north. TP brings perspectives as a cis-gendered male, white, settler public health physician in Canada. He led this work and the analysis and is trained at a graduate level in qualitative and other research methods. While the author group strived to be reflexive on position and perspective in this analysis, their perspectives provide expertise but also represent values regarding guidelines and EMLs, which may influence the perspective brought to the analysis.

Sample Applications for User-Experience Input

We selected two real EML applications from the 2021 Expert Committee meeting based on representativeness of the medicines and important topics in consultation with the WHO Secretariat of the Expert Committee. The applications focused on long-acting insulin analogues (e.g. glargine) for diabetes and immune checkpoint inhibitors (e.g. pembrolizumab) for non-small cell lung cancer (NSLC) (14). Both applications were typical applications to add medicines into the EML, addressing the merits of the medicine in long text form and in that they were not directly linked to guidelines and had not used an EtD framework (appendix 2 and 3). To test usability of the EtD framework, we created 8-page summary EtD frameworks to capture content related to the decision criteria. The decision criteria included in the EtD were those from the traditional GRADE EtD for interventions (15, 16). The decision criteria linking the guideline EtD criteria and EML application are presented in figure 1 from previous work (4).

Figure 1. Decision criteria for guideline EtDs and mapping onto EML decision criteria (4).

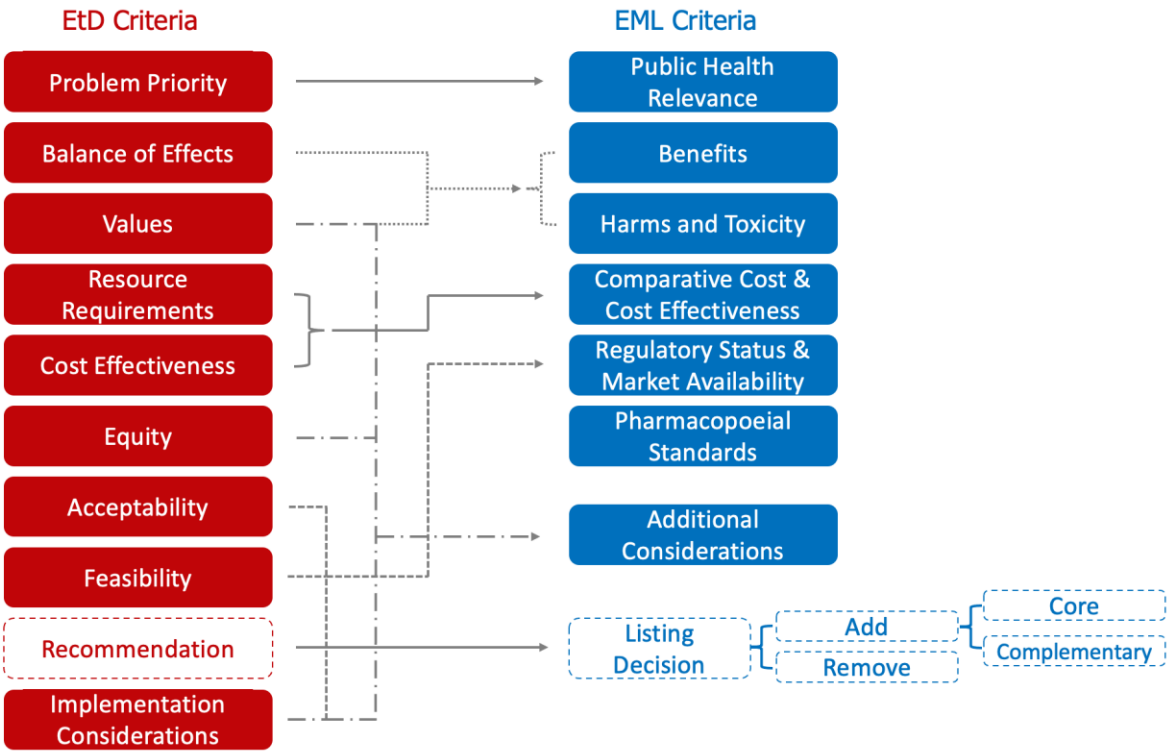

Figure 1 description: this figure visualizes the decision criteria for guideline evidence-to-decision processes and EML applications. Solid lines draw connections between EtD criteria and EML criteria. Dashed lines highlight decision criteria, for a guideline this is a recommendation (strong or conditional), for an EML this is a listing decision. Listing decisions can be to add or remove a medicine from the EML.

For each EML application we completed searches between May 22 – 30 2021 for existing systematic reviews on each decision criteria utilizing the Living Overview of Evidence (L·OVE) platform (Epistemonikos Foundation, Santiago, Chile). We integrated results into the EtD framework table to support judgements on EtD criteria (TP). In a guideline these judgements across EtD criteria would traditionally be made by consensus of the guideline panel, however, no panel was struck for the sample application we prepared, so based on the evidence, judgements were proposed by one researcher (TP) and subsequently reviewed by two other

team members (HJS, LM). No changes to judgements on the EtD criteria (e.g. desirable, undesirable effects, equity etc.) were suggested at review. To visually summarize content and EtD criteria we also developed 1-page summary visual abstract of the EtD frameworks with input from a visualization expert (CC).

Respondent Recruitment

Our target population included both users of EML applications (committee members) and individuals preparing applications to EMLs (applicants). In collaboration with the WHO Secretariat of the Expert Committee staff we developed an initial list of stakeholders comprised of both current and former committee members and current and former applicants. We developed the list and invited individuals with attention to diversity across geographic, gender, racial, organization-type, and professional backgrounds to ensure equitable stakeholder input. We piloted the user-experience interviews (see below) with three committee members prior to the 2021 MLEM Expert Committee meeting to ensure their input on the application materials was not 'contaminated' by discussions at the 2021 MLEM Expert Committee meeting. We followed up with these three members following the 2021 MLEM Expert Committee meeting to assess how their perspectives had changed experiencing these applications. Subsequently we sent invitations via e-mail (with up to 2 follow-up invitations if no response) to complete user-experience interviews using our initial list of respondents and identifying additional respondents through respondent-driven sampling. We continued interviews until reaching consensus on data saturation across user-experience honeycomb dimensions.

User-Experience Testing Interviews

We recruited respondents for a video conferencing meeting via Zoom (Zoom Video Communications, California, USA). Prior to the meeting we shared six documents for the respondents to review. They included traditional EML application, EtD framework, and 1-page

visualization of EtD framework for two 2021 WHO MLEM applications: checkpoint inhibitors for lung cancer, and long-acting insulin analogues for diabetes. We began interviews with screen-sharing and observation of interviewee review and interaction with the supplied documents. We then asked questions from a pre-developed semi-structured interview guide (available in Appendix 1). The interview guide questions followed inquiry into Morville's dimensions of usability: valuable, useful, usable, findable, credible, accessible, and desirable (11).

User-Experience Qualitative Data Analysis

The primary interviewer (TP) engaged in journaling to support reflexive analysis after each interview and reviewed the information with the authorship group at several stages through the interview recruitment process. We audio recorded and transcribed them verbatim. Furthermore, we returned to interviewees if any clarification was required at the time of analysis. We then deidentified transcripts and uploaded them to NVIVO (v2022, QSR International, Melbourne, Australia) for qualitative data analysis which included review and coding by two interviewers according to Morville's dimensions (11). Finally, coded and classified quotes were thematically analysed using a deductive approach centred on Morville's usability honeycomb and to opportunities to improve the proposed Evidence-to-Decision and visual abstract. We also coded quotes referring to feedback to improve either the EtD or visual abstract.

Refinement of EtD and visual abstract for EMLs based on User-Experience Analysis

The EtD for EML applications was iteratively refined in sequential meetings by a core project group (TP, LM, HJS, BH), based on interviews, until satisfied that all themes around improving usability were adequately addressed.

Results

We identified and invited 18 potential users to participate: 13 individuals participated (response rate of 72%), 4 of whom we interviewed in a second follow-up interview, for a total of 17 interviews. Interviews ranged in duration between 41:35 and 52:57 minutes.

Table 1. User-experience Interview Respondent Characteristics (see also appendix 5).

Characteristic	Characteristic	Number	Percentage
Gender	Female	5	38%
	Male	8	62%
	Other/Not Reported	0	0%
Perspective	WHO MLEM Member	3	23%
	WHO Staff	2	15%
	National EML Member	1	7%
	MLEM Applicant	7	54%
WHO Region of Work	AFRO	1	8%
	EMRO	1	8%
	EURO	4	33%
	PAHO	6	50%
	SEARO	1	8%
	WPRO	0	0%

Coding

Coding using the pre-established user-experience honeycomb model yielded 103 instances of coding across all interviews, with variability in coding volume from 1 to 23 instances across all interviews and a median of 7 codes per interview and 8.5 codes per coding category.

Table 2. Coding frequency table

Interviewee #	A	B	C	D	E	F	G	H	I	J	K	L	TOTAL
1	0	2	1	2	2	2	0	2	0	1	0	1	13
2	0	0	0	0	0	2	0	1	1	0	0	0	4
3	0	0	0	1	0	1	2	2	2	0	0	0	8
4	1	4	0	1	2	3	0	6	2	2	2	0	23
5	0	0	0	0	0	0	0	0	1	0	0	0	1
6	0	0	0	1	1	0	0	1	1	0	0	0	4
7	0	2	1	0	1	0	1	2	0	1	0	0	8
8	0	0	1	2	1	0	2	0	0	0	2	1	9
9	0	0	2	1	0	1	2	1	1	4	1	1	14
10	0	0	0	0	0	0	0	2	1	1	0	2	6
11	0	1	0	0	0	1	1	1	1	0	1	1	7
12	0	1	0	0	0	1	1	0	0	0	1	0	4
13	0	0	1	0	0	0	0	0	0	0	0	1	2
TOTAL	1	10	6	8	7	11	9	18	10	9	7	7	103

Table caption: A-Accessible, B-Credible, C-Desirable, D-Findable, E-Usable, F-Useful, G-visual abstract feedback, H-EtD feedback, I-traditional application feedback, J-applicant instructions, K-committee instructions, L-link to national EML.

User-Experience Qualitative Data Analysis

The user experience of respondents yielded findings across all dimensions of Morville's user-experience honeycomb. Key quotes supporting feedback across each dimension are included in appendix 6. User experience findings are also visually summarized in the honeycomb model in Figure 2.

Figure 2. Key Findings Grouped by Morville Honeycomb Model of User Experience

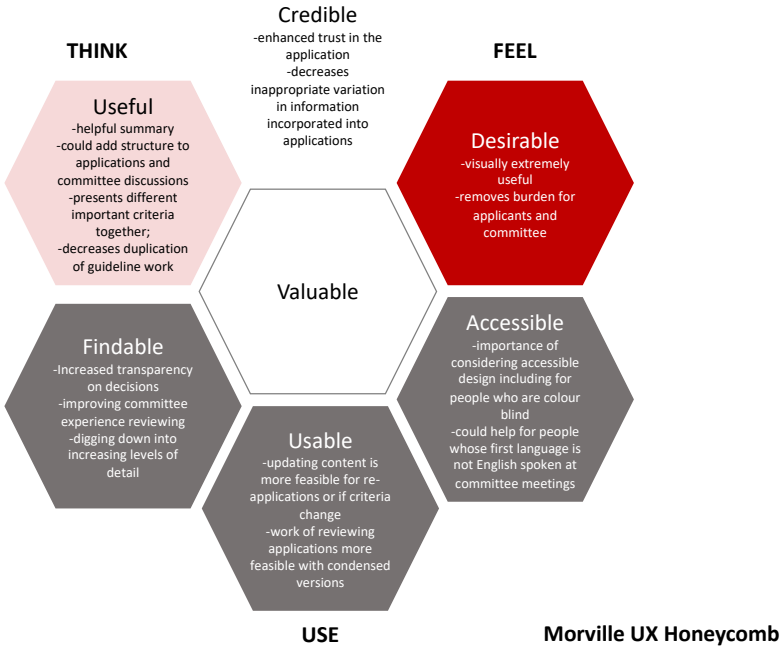

Figure 2 description: This figure shows dimensions of the Morville user-experience honeycomb model and key themes identified under each through thematic analysis. The grey are the 'use' dimensions, light red are the 'think' dimensions and dark red 'feel' dimensions in the user-experience honeycomb model. Notably this includes that the EtD framework and visual abstract were found to be visually useful, more credibly incorporate evidence and useful for expert committee reviews and discussions.

Content of the EtD framework for EML applications

On the basis of feedback from participants we made changes to the EtD criteria. The decision-criteria in for our proposed EtD for EMLs blends criteria in the original GRADE EtD and the decision-criteria used by the WHO EML. We changed problem priority to public health relevance, labelled desirable/undesirable effects as benefits/harms and toxicity, and added a separate criterion for availability. Values was suggested as a possible criterion for an EtD for EMLs. The decision proposed is: Should this medicine be on the EML: yes, list the medicine; no, do not list the medicine; remove the medicine (if already on the list); list the medicine under certain conditions (list the conditions, e.g. price reduction, research settings only). Conditional listing is not currently part of the WHO MLEM, but may be part of national EMLs. The criteria are presented in table 3.

Table 3. EtD for EML Decision-Criteria, Descriptions and Judgements

EtD for EML Criteria	**Description**	**Judgements**
Public Health Relevance	Is the medicine being evaluated for a condition of important public health relevance?	• No • Probably No • Probably Yes • Yes • Varies (if so, why?) • Don't know
Benefits (desirable effects)	How substantial are the benefits?	• Trivial • Small • Moderate • Large • Varies (if so, why?) • Don't know
Harms and toxicity (undesirable effects)	How substantial are the harms and toxicity?	• Trivial • Small • Moderate • Large • Varies (if so, why?) • Don't know

Certainty of evidence	What is the overall certainty of the evidence of effects?	• Very Low • Low • Moderate • High • No included studies
Values	Is there important uncertainty in how people value the main outcomes?	• Important uncertainty • Possibly important uncertainty • Probably no important uncertainty • No important uncertainty
Balance of Effects	Does the balance of effects favour the medicine being considered an essential medicine?	• No • Probably No • Probably Yes • Yes • Varies (if so, why?) • Don't know
Resources required (costs)	How large are the resources required (costs)	• Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies (if so, why?) • Don't know
Cost effectiveness	Does the cost-effectiveness favour the medicine?	• Favours the medicine • Probably favours the medicine • Does not favour either the medicine or no medicine • Probably does not favour the medicine • Does not favour the medicine • Varies (if so, why?) • Don't know
Equity	What would the impact of listing the medicine be on health equity?	• Reduced • Probably reduced • Probably increased • Increased • Varies (if so, why?) • Don't know
Acceptability	Is the medicine acceptable to key stakeholders?	• No • Probably No • Probably Yes • Yes • Varies (if so, why?) • Don't know
Feasibility	Is the medicine feasible to implement?	• No • Probably No • Probably Yes • Yes • Varies (if so, why?)

		• Don’t know
Availability	What is the regulatory status, market availability and on-the-ground availability/access of the medicine to patients?	• Not available in most settings • Probably not available in most settings • Probably available in most settings • Available in most settings • Varies (if so, why?) • Don’t know
Decision	Should this medicine be on the EML?	• Yes, list the medicine • No, do not list the medicine • Remove the medicine (if already on the list) • List the medicine under certain conditions (list conditions)

Summary of the information

Respondents found the products created to complement the traditional EML application, the EtD framework and visual abstract, valuable and several were emphatic on the added value. They felt given the burden of applications (nearly 90 to the WHO MLEM in 2021), it is important to have tools that can summarize the diversity of and quantity of evidence. Respondents generally felt all three products, visual abstract, EtD framework and full application should be consistent with one another and would serve different purposes depending on the level of detailed desired. Committee members assigned to reviewing and presenting the applications may make use of the full application with all its details, however other committee members, health care providers, and the general public may prefer abbreviated versions and only refer to the detailed information if they needed the specific details contained therein.

Overall, respondents felt greater methodological rigour is needed for EML applications. Respondents found the products added clarity and transparency. They also felt transparency may support implementation at the health system and health care provider level. Respondents articulated that established reporting checklists should be used as appropriate, e.g. PRISMA checklist for systematic reviews that inform applications. Further, incorporation of perspective, in

particular patient/public who are impacted by EML applications was highlighted as an important suggestion. They mentioned that if applications are linked closely to existing systematic reviews or guidelines created for other purposes, they might reduce duplication of work and improve consistency of evidence synthesis across products. Finally, attention to accessibility of products was noted as important including for those who are colour-blind or whose first language is not English (as this was the language of preparation of materials).

Feedback and suggested changes to EtD framework

We incorporated suggested changes and improvements into the EtD framework presented in table 3. Feedback centered on instructions on how to prepare the application in particular for the newly added 'availability' criteria. There was feedback around how availability of medicines should be operationalized and whether it should be a criterion for determining recommendations similar to feasibility, or an implementing consideration following the recommend. The feedback for the most part supported separation of availability into a separate domain, since it is a separate criterion assessed in the WHO EML application. They felt the framework would also be useful to support EML Expert Committee discussions and decisions through more succinct summary evidence than contained in traditional applications.

Feedback and suggested changes to visual abstract

Respondents provided constructive feedback to the visual abstract which we subsequently incorporated. Feedback is compiled visually in figure 3. One suggestion was to add a section on current status of medicine with options including: listed, not listed, listed for other indication. Design improvements included selection of icons that were more relevant, improved readability of text, and balanced details and brevity in content provided under each domain. Respondents suggested the prompting of content for consistency and easy access to information including a

"fill in the blanks" approach to criteria. They felt that the transparent communication of who was making judgements was quite important to EML processes: are these judgements for applicants to propose or EML Expert Committee members to make?

Figure 3 Revised visual abstract with respondent feedback displayed.

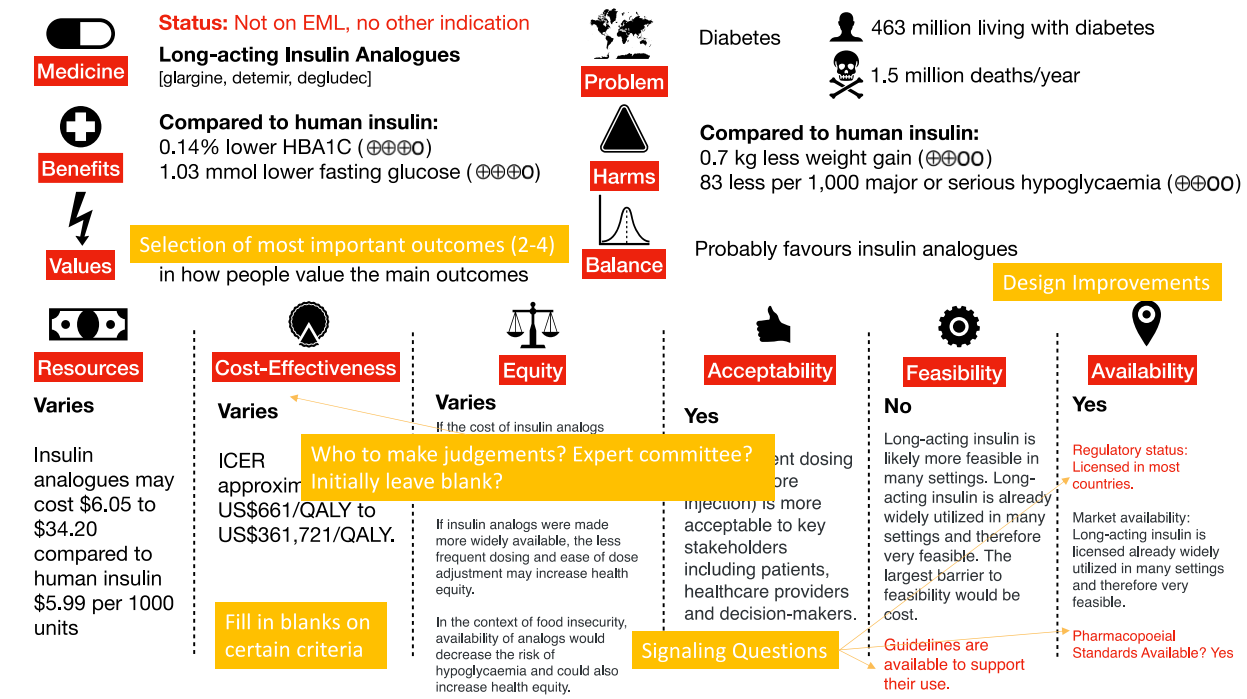

Figure 3 description: The initial draft visual abstract was revised where yellow boxes show suggestions from respondents and red text shows additional text based on suggestions. "Availability" is added here as a new criterion specific for EML application.

Feedback on Instructions to EML applicants

Our interview respondents reviewed the EtD framework and input to improve these products was incorporated. A key point of feedback from applicants interviewed was around the clarity of instructions that accompany these product to applicants, and the original application. Applicants felt greater clarity in expectations and format from the WHO secretariat is important so that they

could prepare the most effective application possible. Expert committee members on the other hand felt there is a balance in communicating instructions to EML applicants. They felt more directed guidance on applications may improve the quality and consistency of applications. However, they also were concerned that more instructions and rigidity could dissuade potentially valuable/important applications – submission of applications is open to any interested party including those that might not have scientific background - or create the wrong perception that significant resources or GRADE/guideline expertise are required to create an application.

For specific domains respondents felt greater clarity in instructions would be important. For example, how should cost and cost-effectiveness be considered? What settings must be reviewed/included? What methods for the estimate of cost/cost-effectiveness are appropriate.

Feedback on Instructions to EML Committee Members for Review and Decision on Applications

Respondents emphasized the challenging task that EML Committee members have to review many applications within a relatively short timeframe and make recommendations on the upkeep of a list, at the WHO-level, now over 400 medicines long. Applications may have been previously considered by an EML committee. Documentation and clarity on previous deliberations, in addition to new evidence, is important to EML decision-making. The appointment of members, the WHO expert committee, also present a challenge and opportunity in terms of EML group process. One respondent suggested standardized training in evidence assessment would be helpful to Committee members. Respondents also suggested feedback to applicants is also important to future development of research to inform essential medicine selection. For example, if a primary barrier to listing a medicine was cost effectiveness or feasibility, feedback for what would need to change, or what additional information would be helpful is critical to improving future applications. Finally, additional instructions on how

applications could be assessed in a more standardized way, e.g. the use of the AGREE tool for quality appraisal of guidelines, or development of a new tool.

Discussion

In this qualitative study of user experience of EML applications we observed that creation of EtD frameworks, and 1-page visualizations could support decisions by EML applicants and Expert Committee members. Our results also highlight the importance of improving the coordination and connection between EMLs and guidelines, extending our previous findings which found that closely linking both processes could generate important synergy and decrease the duplication of work (4).

Strength and Limitations

As a strength, this study applies a qualitative systematic methodology, grounded in Morville's user-experience honeycomb model, mostly used in information technology science to an important health care prioritization tool – the selection of essential medicines. We were able to work directly with decision makers and applicants to inform and improve their experience and comprehensively build upon themes that have begun to emerge from previous works (4, 17-19). Together, these findings should inform future methodological and group process improvements for EMLs at the global and national level.

Limitations of this study include that a relatively large number of respondents were from the WHO EURO and PAHO regions. We were unable to recruit respondents from the WPRO region and only two respondents from national EML perspectives. While we sought to equitably engage diverse perspectives in purposeful sampling this was not fully achieved given the

preponderance to global north perspectives in our author group, and future work should seek to draw from these regions to obtain more perspectives and complete further testing across settings. In terms of feasibility, the creation of visual abstracts and EtDs would place an additional work burden, particularly for nearly 90 applications, on the applicant or WHO staff, unless already produced for a guideline. This should be further assessed to determine methods of implementation, which may include prioritizing topics for applications that would most benefit by EtD/visual abstract information. However, the additional perceived burden should be worth the expected overall efficiencies through less duplication of work between guidelines and EMLs.

Implications for practice and policy

Improved clarity for EML applicants and improved trustworthiness of the EML is a topic of significant interest to the WHO EML Secretariat and national EMLs globally (4). The trustworthiness and criteria used to select medicines for the WHO EML has recently been subject of increased attention and critique (20). Globally, with significant divergence of national EMLs and notable gaps from the WHO Model List of Essential Medicines, there is room to improve the methods and rigour of EML selection and the ease with which these can be adopted or adapted for national EMLs (21, 22). Medicines on the EML should also influence guideline development recommendations so that all medicines on the EML are supported by trustworthy guidelines.

Since 2017 the MLEM is providing applicants with an application template word document. Based on a positive response to the EtD framework and visual abstracts we have created here, resources providing guidance to future applicants and supporting EML Committee members can be further expanded and updated. At the WHO level the provision of instructions and templates should be balanced with the need to maintain flexibility so that decisions may continue to be

made based on the merit of medicines and not the resources available to develop the quality of the application. Nonetheless, opportunities to improve the methodological rigour and transparency in communication should be taken.

This work provides support for the connection of various paradigms of evidence synthesis for health decision-making (10, 18). Work to develop the immune checkpoint inhibitors EtD and the visual abstract identified a Cochrane Systematic Review that addressed the same PICO question and was published the same month as the ESMO-sponsored EML application was submitted, but without an underlying systematic review. This duplication of work provides evidence for the need to better coordinate efforts to synthesize evidence for health decision-making.

Implications for research

Our work raises additional questions on the connections between EML and other evidence-synthesis products more broadly. Further research on the feasibility, risks and benefits of aligning these processes is important. Specifically relating to the use of EtD frameworks and visual abstracts, further work should assess process to understand feasibility, desirability and benefit of this work at national levels due to our focus on the WHO Model List. Thus, it is important to address the wide variability in national EMLs, including better understanding of the processes that underlain local medicine recommendations. Further research should explore the different national country contexts for EML globally, and whether improved usability and evidence synthesis to support EML applications, as we have communicated here, will translate to better decisions.

Conclusions

We have presented solutions to improve the methodological rigour and user-experience of applicants and Committee members for EMLs, with a focus on WHOs MLEM. We found that usability could be improved through adjunctive products such as EtD frameworks and visual abstracts. Developing these products could be developed in conjunction with linked guidelines and systematic reviews can harmonize these products, decrease duplication of work, and lead ultimately to better health decision-making and access to essential medicines.

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LETTER OF INFORMATION / CONSENT

Exploring the Decision-Making Process for the Selection of Essential Medicines

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Purpose of the Study

You are invited to take part in this study on development of an Evidence-to-Decision making framework to support selection of Essential Medicines as an expert. The purpose of the study is to explore how an evidence to decision framework could be developed and applied to support the selection of essential medicines in the Model Essential Medicine List of the World Health Organization and National Essential Medicine Lists.

Procedures involved in the Research

The study will involve one qualitative interview lasting approximately 30-45 minutes. With your permission we hope to audio-tape the interview and later transcribe the recording. There will be several prepared questions, however, it is hoped that the interview can be more open-ended as to gain insight to your perspective on these matters. You may also be asked to use a prototype software program, while sharing your screen to test your experience and the usability of this program. The following is an example of an interview question:
- Given your knowledge and experiences with essential medicine lists, could you please begin by describing how decisions regarding the addition, maintenance, or removal of medicines from an essential medicine lists (MEML or National EML) are made?

Potential Harms, Risks or Discomforts

The risks involved in participating in this study are minimal. You may feel uncomfortable answering questions surrounding your knowledge or experiences with evidence to decision frameworks or essential medicine lists. In the event that this happens, you do not need to answer any questions that you are uncomfortable with and you can withdraw at any time during the interview. The steps taken to protect your privacy are described below.

Potential Benefits

The research will not benefit you directly. We hope to learn more about the process of selecting essential medicines. It is hoped that this will lead to the development of a framework that can be utilized by the World Health Organization and other organizations to develop essential medicine lists.

Confidentiality

You are participating in this study confidentially. Your name or any information that would allow you to be identified will be protected. No one but the researcher will know whether you participated unless you choose to tell them.

The information/data you provide will be transcribed and dissociated with your name and identity. The transcript will be kept on a password-protected computer. Once the study has been completed, the data will be destroyed.

Participation and Withdrawal

Your participation in this study is voluntary. If you decide to be part of the study, you can decide to stop (withdraw), at any time, even after signing the consent form or part-way through the study. If you decide to withdraw, there will be no consequences to you. If you wish to withdraw, please contact the research coordinator at: piggott@mcmaster.ca or by phone at 905-746-0235.

Information about the Study Results

We expect to have this study completed by approximately December 2020. If you would like a brief summary of the results, please inform us how you would like them sent to you.

Questions about the Study

If you have questions or need more information about the study itself, please contact the research coordinator at: piggott@mcmaster.ca or by phone at 905-746-0235.

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HiREB). The HiREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call The Office of the Chair of HiREB at 905.521.2100 x 42013.

CONSENT

I have read the information presented in the information letter about a study being conducted by Dr. Thomas Piggott and Dr. Holger Schünemann, of McMaster University.
I have had the opportunity to ask questions about my involvement in this study and to receive additional details I requested.
I understand that if I agree to participate in this study, I may withdraw from the study at any time. I will been given a signed copy of this form. I agree to participate in the study.

1. I agree that the interview can be audio/video recorded. *Yes* *No*

_____	_____	_____
Name of Participant (Printed)	Signature	Date
Consent form explained by:		
_____	_____	_____
Name and Role (Printed)	Signature	Date

User Testing of an Evidence-to-Decision making Framework to Support Selection of Essential Medicines

Interview Guide

A. Participant Information

Participant no.:	
Participant name and contact information:	Name: Email/Telephone:
Location:	
Date:	
Interviewer/Note-taker:	
Recorder interview no.:	

B. Interviewer Checklist

For in person interviews:

- Confirm the date, time and location of the meeting. Send a reminder to the participant before the meeting.
- Printed copy of Interview Guide. Take notes (point-form preferred) in the spaces provided.
- Printed copy of draft list of items generated.
- Additional paper to take notes if needed.
- Audio recorder. Test the recorder before each interview.

For interviews by telephone or online Zoom:

- Make sure you have the land line phone number or have set up the Zoom
- For interviews by Zoom, share the meeting link with the interviewee in advance; send the PDF of the draft list of items generated.
- Confirm the date and time of the call. Send a reminder to the participant before the meeting.
- Interview Guide form to take notes. Additional paper to take notes if needed.
- Audio recorder. Test the recorder before each interview.

C. Introduction and Consent Statement

Say: Thank you very much for agreeing to participate in this interview. We are asking colleagues and other people who have been involved in the development or use of essential medicine lists their views on the current process and the potential use of a framework to assist with making medicine recommendations.

We will use your input to support this work to help support decision-making by for essential medicine lists. Our hope is that this can support the development of more rigorous and trustworthy essential medicine lists.

Participant Consent Statement:

Say: The research study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). With your permission, the session will be recorded on tape for transcription and erased after the transcription has occurred. Transcribed data will be analyzed and coded into themes, and destroyed at the end of the study period and publication. De-identified coded themes will be destroyed after a period of 5 years. You may also withdraw your responses from the interview at any time.
Do you agree for the data collected in the study to be used anonymously in publication?

☐ Yes ☐ No Notes:

Do you also agree to have the interview recorded?

☐ Yes ☐ No Notes:

Ask: Do you have any questions before we proceed?

D. Questions

Involvement in National EML;
Duration of time involved in MLEM;
Professional background;
Cochrane/guideline involvement;

11. Before we begin I would like to just clarify your **current position** and **any involvement** or exposure you have had to **essential medicine lists**?
Prompt: What about the WHO MLEM? Duration of time on the Expert Committee?

Say: To date, we have reviewed the literature and consulted experts involved in the development of essential medicine lists. This led to the development of two draft Evidence-to-Decision frameworks on EML topics to support the decision-making process. We have shared these, as well as the two traditional applications documents, with you in advance of the meeting.

12. Comparing the Insulin Analogues application document and EtD 1: Insulin Analogues, what is your perspective on the usability for the Expert Committee in relation to the traditional application? [Share screen]
    Prompt: User-Experience Honeycomb - Is information useful? Usable? Desirable? Findable? Accessible? Credible? Valuable?

13. Looking at the Anti-PD1/PD-L1 antibodies application document and EtD 2: Anti-PD1/PD-L1 antibodies, what is your perspective on the usability for the Expert Committee in relation to the traditional application? [Share screen]
    Prompt User-Experience *Honeycomb - Is information useful? Usable? Desirable? Findable? Accessible? Credible? Valuable?*

Additional Question Bank

14. In what ways could using this EtD and presentation improve the consideration of the evidence by the expert committee?

15. In what ways could using this EtD and presentation hinder the consideration of the evidence by the expert committee?

16. In what ways could using this EtD and presentation affect transparency in MLEM decision-making?

17. In what ways could using this EtD and presentation affect efficiency in MLEM decision-making?

18. In what ways could using this EtD and presentation impact support national EML decision-making?

19. Should this type of presentation be used more routinely in the consideration of medicines for EMLs? Should a modified GRADEpro system be used to help?

F. End of Interview

Say: Thank you very much for your participation and feedback.

Chapter 3: Appendix 2: Application Example 1 - Anti-PD1/PD-L1 antibodies for Lung Cancer

Anti-PD1 Inhibitors
[nivolumab, pembrolizumab]

Compared to chemotherapy (per 1,000):
119 fewer deaths (⊕⊕⊕O)
16 more progression free survival (⊕⊕OO)
115 more overall response rate (⊕⊕OO)
135 more higher Quality of Life (⊕⊕OO)

No important uncertainty or variability in how people value the main outcomes

Lung Cancer 2 million cases/year
1.8 million deaths/year

Compared to chemotherapy (per 1,000):
244 fewer grade 3/4 adverse events (⊕⊕OO)

Favours Anti-PD1 Inhibitors vs chemotherapy

Large Costs

Drug costs alone over $100,000 per patient.

Lung CA prevalent and therefore budget impact higher than for less common cancers.

Favours chemotherapy

ICER approximately $100,000 per QALY gained

Reduced

If this drug is listed it would decrease health equity unless pricing decreases substantially.

Probably Yes

These drugs are likely acceptable to patients and healthcare providers due to effectiveness and less undesirable effects than alternative regimens.

These drugs are likely not acceptable to decision-makers in most settings due to the cost.

No

This intervention is feasible and already implemented in many high-income settings.

Globally this intervention is not currently feasible across most settings.

QUESTION

Should anti-PD1 immune-checkpoint inhibitors vs. chemotherapy be used for "non-oncogene- addicted" (EGFR, ALK, and ROS1 wild type) locally advanced and metastatic non-small cell lung cancer (NSCLC)?	
POPULATION:	"non-oncogene- addicted" (EGFR, ALK, and ROS1 wild type) locally advanced and metastatic non-small cell lung cancer (NSCLC)
INTERVENTION:	anti-PD1 immune-checkpoint inhibitors
COMPARISON:	chemotherapy
MAIN OUTCOMES:	Overall survival; Progression-free survival; Overall response rate; Adverse Events grade 3-4; Quality of Life;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**From Pentheroudakis MLEM Application** Lung cancer is the most diagnosed and the first cause of death for cancer worldwide, estimating 2 million new cases and 1.7 related deaths in 2018, according to Global Cancer Observatory 2018 (5). Lung cancer is a highly lethal malignancy, with an economic impact estimated around $8 billion productivity lost in the BRICS countries (6). Moreover, in the absence of a wide coverage of an effective screening programme in place on global scale, lung cancer diagnoses occur in advanced stages (i.e. III and IV, TNM 8th) in more than 60% of cases, with highly regional variability (7-9). Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide. Over 80% of the lung cancers are classified as NSCLC. Although targeted therapies have redefined the therapeutic landscape for patients with molecularly druggable NSCLC (e.g. epidermal growth factor receptor [EGFR] mutations, anaplastic lymphoma kinase [ALK] rearrangements, ROS1 rearrangements, BRAF mutations, HER2 mutations or amplifications, NTRK1-3 fusions), these therapies are ineffective in those tumours lacking such genetic alterations, the majority of NSCLC patients. However, ICI therapy has become part of the treatment of such patients, which has led to improvements in survival and quality of life. The ICI target and reactivate the immune-competent cells, i.e. T-lymphocytes and antigen-presenting cells, by inhibiting the immunosuppressive ligand PD-L1 or its receptor, PD-1, in the tumour-induced immunosuppressant milieu or by strengthening the immune-activating signals of immune-response (e.g. GITR, pro-inflammatory interleukins, interferon-gamma) (10). The approval of ICIs in NSCLC addresses an unmet need for patients considered to have a poor prognosis in advanced stage, in the absence of an indication of targeted therapy." **Desirable Effects** How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**From Dec 2020 Cochrane Review** https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013257.pub2/full	Evidence from original application. Large desirable effects for expression ≥50%.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with chemotherapy	Risk difference with anti-PD1 immune-checkpoint inhibitors

Full application available:

https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee/a.1-anti-pd1-immune

Appendix 3: Application Example 2 – Long-Acting Insulin Analogues for Diabetes (see file)

Long-acting Insulin Analogues
[glargine, detemir, degludec]

Diabetes

463 million living with diabetes

1.5 million deaths/year

Compared to human insulin:
0.14% lower HBA1C (⊕⊕⊕O)
1.03 mmol lower fasting glucose (⊕⊕⊕O)

Compared to human insulin:
0.7 kg less weight gain (⊕⊕OO)
83 less per 1,000 major or serious hypoglycaemia (⊕⊕OO)

Probably important uncertainty or variability in how people value the main outcomes

Probably favours insulin analogues

Varies

Insulin analogues may cost $6.05 to $34.20 compared to human insulin $5.99 per 1000 units

Varies

ICER approximately US$661/QALY to US$361,721/QALY.

Varies

If the cost of insulin analogs remains more expensive or access is reduced to human insulin this would probably reduce health equity.

If insulin analogs were made more widely available, the less frequent dosing and ease of dose adjustment may increase health equity.

In the context of food insecurity, availability of analogs would decrease the risk of hypoglycaemia and could also increase health equity.

Yes

Less frequent dosing (and therefore injection) is more acceptable to key stakeholders including patients, healthcare providers and decision-makers.

No

Long-acting insulin is likely more feasible in many settings.

Long-acting insulin is already widely utilized in many settings and therefore very feasible. The largest barrier to feasibility would be cost.

QUESTION

Should long-acting insulin analogs vs. human insulin be used for diabetes?	
POPULATION:	diabetes
INTERVENTION:	long-acting insulin analogs
COMPARISON:	human insulin
MAIN OUTCOMES:	HBA1C reduction - Type 1 DM (Tricco); Fasting plasma glucose; Weight gain; Major or serious hypoglycemia;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**From application (Dzintars Gotham):** Diabetes affected an estimated 463 million people in 2019, or 9.3% of the global population, of which 79% live in low- and middle-income countries (LMICs).(12) It was responsible for over 1.5 million deaths and 2.79% of all global disability-adjusted life years lost (DALYs) in 2019.(13) It is estimated that diabetes reduces life expectancy by 6 years when diagnosed at the age of 40.(9) Diabetes also significantly increases the risk of other non-communicable diseases, including heart disease and cancer.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Recent meta-analyses have found benefits for (ultra-)long-acting insulins in terms of reducing hypoglycaemic episodes and improvement in glycaemic control. The findings of these meta-analyses are more pronounced than those available at the time of earlier EML Expert Committee reviews of insulin analogues. Overall, the effect size and evidence base is arguably stronger for use in type 1 diabetes than for use in type 2 diabetes, and stronger for long-acting insulins (glargine and detemir) than for ultra-long-acting insulin (degludec). Network Meta-analysis by Tricco et al (2021) covering 64 RCTs found that long-acting analogues led to fewer major or serious hypoglycaemic episodes (OR 0.63, 95%CI 0.51-0.79), nocturnal hypoglycaemic episodes (OR 0.74, 95%CI 0.58-0.94), reduction in HbA1c (mean difference -0.14 percentage points (95%CI -0.22 – -0.06), fasting plasma glucose reduction (mean difference -1.03 mmol/L (95%CI -1.33 – -0.73), and weight change (mean difference -0.70 kg (95%CI -1.08 – -0.32). The NMA found no significant difference for all-cause hypoglycemia, vascular complications, microvascular complications, macrovascular complications, any adverse events, serious adverse events, and drop-outs due to adverse events. **Tricco 2021**	

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

Full application available:

https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/23rd-expert-committee/a20-long-acting-insulin

Chapter 3: Appendix 4: COREQ Checklist (23)

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	10
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	10
Occupation	3	What was their occupation at the time of the study?	10
Gender	4	Was the researcher male or female?	10
Experience and training	5	What experience or training did the researcher have?	10
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	9
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	9
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	10
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	11
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	9-10
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	9
Sample size	12	How many participants were in the study?	11
Non-participation	13	How many people refused to participate or dropped out? Reasons?	11
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	10
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	10
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	11-12
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	10
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	11
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	11
Field notes	20	Were field notes made during and/or after the inter view or focus group?	11
Duration	21	What was the duration of the inter views or focus group?	11
Data saturation	22	Was data saturation discussed?	10
Transcripts returned	23	Were transcripts returned to participants for comment and/or	11

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	11
Description of the coding tree	25	Did authors provide a description of the coding tree?	12
Derivation of themes	26	Were themes identified in advance or derived from the data?	11,13
Software	27	What software, if applicable, was used to manage the data?	11
Participant checking	28	Did participants provide feedback on the findings?	11
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	35
Data and findings consistent	30	Was there consistency between the data presented and the findings?	13
Clarity of major themes	31	Were major themes clearly presented in the findings?	13
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	13-20

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

Chapter 3: Appendix 5: Respondent characteristics

INTERVIEWEE	GENDER	ROLE	WHO REGION OF WORK
1	M	WHO Staff	EURO
2	M	WHO Staff	EURO
3	F	MLEM Expert Committee Member	EURO
4	M	MLEM Expert Committee Member	PAHO
5	M	MLEM Applicant	PAHO
6	F	MLEM Applicant	PAHO
7	M	MLEM Applicant	PAHO
8	F	MLEM Applicant	PAHO
9	M	MLEM Applicant	EURO
10	M	MLEM Applicant	PAHO
11	F	MLEM Applicant	SEARO
12	F	National EML Committee Member	AFRO
13	M	National EML Committee Member	EMRO

Chapter 3: Appendix 6: Key Quotes

- Findable: EtD provides helpful summary of evidence in a more findable way to EML decision-making than longer application;
    - "A high-level summary [like this visual abstract], but then being able to dig down, you find sometimes the panel is happy with high level and then sometimes they really want more detail." [Interview 1]
    - "I can see, this also being really useful and I did wonder about the reviewers experience and going through all of these applications, because I think our applications are also fairly long and that's a lot of material to digest and some of the sections" [Interview 9]
    - "If the goal is to make the process more transparent, having a figure like this that summarizes, people in the public can more clearly say [for example] I disagree with your judgement on equity, I don't think you're harping enough on racial bias. So I think this transparency is a very healthy process." [Interview 12]
- Useful: EtD could allow EML applicants to be more clear on what information the Expert Committee requires for review;
    - "So, in general I think it's a very good approach to make the different dimensions explicit right, because if you have unstructured discussion there is, maybe a tendency to focus on certain aspects and forgetting that another." [Interview 1]
    - "Well, overall, I think the presentation is really useful and it's able to summarize the key information." [Interview 3]
    - "Even on trying to answering a simple question like is this drug already in some WHO guidelines, because then different versions of the guidelines are on the website or it's difficult to find the current version and yeah I think there's room for improvement in trying to keep the different documents aligned." [Interview 5]
    - "Unfortunately, we don't have a lot of capacity to do the reviews, so here in [country] we can't afford to duplicate work and the guidelines and EML need to work together." [Interview 8]
    - "I think, having this kind of information will be very useful because there's no way that I would go read every application right, I mean in the current format." [Interview 9]
- Desirable: Design of the visual abstract could continue to be improved, but is pleasing;

    - “This one-pager [visual abstract] is also visually useful because you know applications are often you know very, very long and cover lot of aspects, so this is a visually extremely useful yeah.” [Interview 7]
    - “Yeah, it’s wonderful, I think it’s really, really sharp, I like the idea of having it in a summarized systematic standardized way. It avoids sort of the descriptive burden, not only for the [EML] committee, but also for the applicants as well” [Interview 4]
    - “the idea of having a standardized way referring to information and avoiding the sort of descriptive pieces removes the burden, not just for the committee members, but also for the applicants as well” [Interview 12]
- Credible: EtD could increase transparency in judgements leading to a decision to accept or reject an application, and feedback to applicants;
    - “I just wonder how much local variation there is, and then impact of this information [in the EtD and visual abstract], because obviously it depends on the disease burden [Interview 2]
    - [With traditional applications if] “you don’t trust the application itself, which is again very difficult because you have to redo something like a new application by yourself. And you have to check why they included some studies and why they excluded other studies, many times, there is no description of the methodology so it’s quite impossible to understand the process.” [Interview 5]
    - “A systematic approach to evidence synthesis could help to increase credibility of applications and trust in evidence presented by applicant.” [Interview 10]
    - “I guess the multi-layer approach is right. Then people have the option, with the audit trail, to go deeper and deeper into the details. I think the different products are useful to a range people.” [Interview 12]
- Usable: EtD could open a process for an online software solution that would make applying and reviewing/managing applications more efficient;
    - “A digital solution would help make the process more efficient, more transparent and more evidence-based” [Interview 1]
    - “The whole application, I think is summarized here [in the visual abstract], and this was very useful, to be honest with you, they assign a few publications for each member to review in detail, you know that's okay that's when we read the entire thing, but they also asked us to review other all other applications, you

know and this would be useful since there are so many other applications." [Interview 4]

- "Well, the first time it's a lot [producing an EML application based on a guideline]. But with updates it becomes more feasible, just like guidelines" [Interview 12]
- "I think more data would be needed [for the EML committee] but then also once a decision is made, the one-pager [visual abstract] could be made available to the public and be very useful" [Interview 12]

- Accessible: multiple products (Full application, EtD (8 pages) and visual abstract summary) would potentially make information more accessible for Expert Committee members who at times struggle with nearly 100 applications per cycle.
    - "And we were writing … during the discussion when my English is not perfect. I have to pay attention to the different people talking during the meetings and That was my first time there and in this document was like a 700 page document that we were filing in a nutshell there, so it was something completely unmanageable so whatever idea you could have for them to streamline the process would be very, very helpful." [Interview 3]

Instructions for EML Applicants

- "So if you want to encourage application from a variety of stakeholders, probably need to find a balance between the super strict methodology, like requiring a systematic review, and then okay, a blank paper, where you can write whatever you want." [Interview 4]
- "Some domains would need like maybe some more guidance, especially you know when talking about cost, comparative cost effectiveness. We actually weren't clear what comparative cost effectiveness actually meant." [Interview 9]
- "I think there should be a requirement to you know, to base the search and synthesis of the available evidence on a systematic review with a protocol that should have at least some basic methodological requirements… to avoid this kind of stuff that we are looking at which is, you know very hard to read." [Interview 9]
- "I have unfortunately never recruited patients to be a part of an application, and that is a regret I do think that it does make an important statement to also have a patient's voice at the table as an author of an application." [Interview 10]

Instructions for EML Committee

- “Whether some basic training it's like a three-hour online module about you know guidelines systematic reviews, meta-analysis, all that, I wonder whether something like that's useful in the future for expert committee,” [Interview 2]
- “the consideration of previous [decisions by Expert Committees on applications for the same medicine], even if the Group then decided to take a different decision, at least [with standardized information and judgements in an EtD] they have the information they need to take it in a in a more informed way to jump back to the previous issue.” [Interview 5]
- “The feedback that we got from [the EML Committee and secretariat] when having discussions was actually quite different from what we got in a written form. Like cost was highlighted to us in our discussions, it was not even mentioned in the in the formal written feedback.” [Interview 11]

Feedback on Traditional EML Application

- “it's information overload right, and I think what our [EML committee] experts suffer from maybe you know, is a certain decision fatigue.” [Interview 1]
- “I can live with the idea that the application is 40 pages, maybe if it's structured a little bit.” [Interview 3]
- “it's really hard for us to go through all these applications. The search will be conducted to make sure that we're not missing any other important evidence either to support or to refute the indication so. So yes, I use either pubmed or use a Google search engine to find additional studies and in areas that I'm not more expert then I'll talk to colleagues that I know who do, you know.” [Interview 4]
- “the first problem is the different format of the application so it's really difficult to navigate through some of the applications, because there are of course there's a kind of list of chapters that has to be taken, but then the content into these chapters is very different from one application to another.” [Interview 3]
- “You don't trust the application itself, which is again very difficult because you have to redo something like a new application by yourself and you have to check why they included some studies and why they excluded other studies, many times, there is no description of the methodology so it's quite impossible to understand the process was false.” [Interview 3]
- “The price is not a state of nature, the price is a policy variable and then, if governments are willing to issue compulsory licenses or you know not have patents on them, or

something like that they can or other measures, they can change the price, and so we thought the there should be a category for something that would be called future price." [Interview 5]

- "You know, say you're a frontline professional in [sub-Sahara Africa Country] and you're interested in this process there's a lot of barriers to actually get involved and to prepare an application it's a pretty heavy lift. And so suppose there is a way to actually create like a network, where people could actually share and collaborate on these applications I've honestly tried to do that over the past 15 years and it's tough, but I want to make sure that every voice is represented." [Interview 10]

Feedback on EtD Framework

- "[Compared to the full application, the EtD is] still a lot, a lot of information to digest I think also probably the human mind has an inherent problem of taking into account and integrating different dimensions right." [Interview 2]
- "Other factors were probably more important in the decision-making process than benefit and harms and those are the situations where really the discussion tends to be a little bit chaotic so having a framework to follow would probably help." [Interview 3]
- "Difficult for for some groups, so if you want to encourage application from a variety of stakeholders, probably need to find a balance between the super strict methodology and then Okay, the blank paper, where you can write whatever you want." [Interview 3]
- "I can see, this also being really useful and I did wonder about the reviewers experience and going through all of these applications, because I think our applications are also fairly long and that's a lot of material to digest" [Interview 8]
- "It's useful to be very clear about the domains we deal with so in applying you can add framework to any application is very useful to be more focused, you know in distinguishing what we know about this drug". [Interview 9]
- "I love the fact that you added a specific domain, which is also because it is a very important aspect, which is access to medicine, the availability is connected to access, which is, I guess, in line with the WHO policy it's a very important topic for the EML community, so I think this is a good addition to the classic EtD." [Interview 9]
- "The idea of having a standardized way of referring to information and avoiding the sort of descriptive pieces removes the burden, not just for the committee members, but also for the applicants as well." [Interview 10]

Feedback on EtD visual abstract

- “This one-pager [visual abstract] is also visually so useful because you know applications are often you know very, very long and cover a lot of aspects, so this is a visually extremely useful yeah.” [Interview 9]
- “I think the explanation is clear and obviously I understand for everything, why we made the decision the explanation is in the summary right there.” [Interview 4]
- “For this is, I didn't quite see a guideline reference here in the table. And then, it raises the question of like which guidelines are the ones that actually are would be focused on right.” [Interview 10]
- “If the goal is to make this more transparent process having a figure like this. That summarizes the criteria and people may disagree with this and say well you know I like the equity piece I don't think you're harping enough on X and you know there's a racial bias, I think those sorts of things is actually a very healthy process so that to me. Is some of the apart from the standardization that kind of making this more publicly available, and it's already it's an incredibly transparent process has is, from my point of view, in terms of posting applications and the comments and the reviews, but I’m just worried that we're not getting enough that as much as we could.” [Interview 12]
- “You have decision fatigue right, you need to make decisions in a relatively constraints timeframe, so your information needs to be accessible quickly if you need to look all kinds of different I read a lot of text it's not going to happen” [Interview 2]

Chapter 4: GRADE concepts: Linking Recommendations to Trustworthy Essential Medicine Lists

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Abstract

Introduction:

Guidelines and essential medicine lists (EMLs) bear similarities and differences in the process that lead to decisions.

Objective:

We sought to explore challenges, and potential solutions for decision-making to support trustworthy essential medicine lists.

Study Design and Setting:

We identified key challenges in connecting EMLs to health guidelines by involving a broad group of stakeholders. We assessed case studies including real applications to the WHO EML, a national EML application in South Africa, and a multiple sclerosis guideline connected to a WHO EML application. We developed draft concepts and potential solutions to connecting EMLs to health guidelines through iterative discussions and refinement in in-person and online meetings and through email communication. To address challenges, we utilized the results of a survey and feedback from the stakeholders. We presented a summary of the results to all attendees of the GRADE Working Group meeting for feedback in November 2022 (approximately 120 people) and in planned in May 2023.

Results:

The challenges and solutions based on our concepts addressing the connection between EMLs and health guidelines focus on the following six domains and EtD criteria: 1. How to improve the connection between systematic reviews, guidelines and EML applications to accelerate access to essential medicines?; What certainty of evidence and strength of recommendation based key decision criteria are essential for the EMLs?; Should availability or cost of a medicine for listing in the EMLs?; How to transparently identify square box indications for medicines, and how should equivalency be assessed by EML applicants?; What is required to support contextualization of the WHO EML to the National level?; and How should EML committees consider equity?

Conclusions:

This GRADE concept article, based on involvement of key stakeholders from the guidelines and EMLs field, identified key conceptual issues and potential solutions to support the continued advancement of trustworthy EMLs. EMLs are an important prioritization tool, at the global and national level. To advance health equity, gaps in availability of essential medicines should be addressed within and between countries by using structured decision criteria that can be linked to guideline recommendations.

Background

Essential medicines are a half-century old concept, with critical modern relevance. Essential medicines should meet priority health needs, be selected based on criteria of public health importance, efficacy, safety, and comparative cost-effectiveness, and are intended to be available at all times in functional health systems [1]. In 1977, the World Health Organization (WHO) issued its first EML with 168 medicines [1]. The landscape of available medicines has changed dramatically since then, however, the need to prioritize effective medicines that should be accessible to everyone worldwide remains. In fact, this need has achieved renewed interest in recent years with the WHO's attention to Universal Health Coverage (UHC), in the broader context of the United Nation's priority of UHC in Sustainable Development Goal 3.8. In its 22nd iteration, the WHO EML has since has now expanded to 479 medicines and a 8th edition of a specialized list for children was released in 2021 [2].

Most countries are expected to improve their national coverage by 2030 offering access to essential medicines, however, there are substantial gaps in selection of medicines at the national level compared with those recommended by WHO, specifically for Africa [3]. Over 137 countries have their own national essential medicine lists (NEMLs) [4]. There is wide variability in the number and nature of medicines included in NEMLs compared to those recommended by WHO, which range from only 44 to as many as 983 included medicines [5]. A degree of contextualization would be expected from country to country due to varied epidemiology and health priorities. However, in analyzing national lists by country and therapeutic class there are

differences that cannot be explained by factors such as disease prevalence, and the linkage to health priorities is not often surfaced as a rationale [5]. Therefore, further work is needed to examine processes and methods to improve transparency and trustworthiness of NEMLs.

Similar to the criticism faced on methodology that did not rigorously incorporate evidence into decision-making for guidelines issued by WHO in the early 2000s, the WHO EML has also been subject to criticism. This criticism has focused on its use of evidence, the composition of the expert committee and its decision-making processes [6-8]. The WHO has made significant progress in the improvement of its guideline methods based on advice from its Advisory Committee for Health Research [9-13]. This has included standardization of processes and adoption of methodologies from the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group [14]. While the WHO EML and national EMLs are distinct from guidelines, there are many parallels in these paradigms as recently demonstrated [15]. We posit that lessons learned from improving trustworthiness of guidelines could be applied to improve production of EMLs.

Pharmacological interventions are very relevant to the GRADE Working Group, with many of the health guideline interventions focused on them. While work by the GRADE Working Group has examined medicine coverage decisions, through the creation of an EtD for coverage decisions, no previous GRADE guidance has focused on essential medicines [16]. Criteria in decision-making for the WHO EML are derived from the revised procedure for updating WHO's Model List of Essential Drugs, approved by the World Health Organization's Executive Board in

2001 [17]. This is therefore the starting point for building a framework to produce an EtD for EMLs, modelled after the GRADE EtD framework. The Executive Board resolution criteria include public health relevance, benefits, harms and toxicity, summary of available data on comparative cost and cost-effectiveness for medicines within the same therapeutic class, regulatory status and market availability, and availability of pharmacopoeial standards. Additionally, a unique feature of the EML is within therapeutic class equivalence listing, denoted by the "square-box" symbol [18]. The "square box" therapeutic equivalence suggests flexibility in implementing at a country-level depending on local price/availability of grouped medicines. Thus, these criteria and our recent work also suggests that there is significant overlap in the decision-criteria that are used by the Expert Committee on the Selection and Use of Essential Medicines for EML decisions and the GRADE Evidence-to-Decision frameworks [19].

Objective

Given the similarities between health guidelines and EMLs, and an understanding of the rigour that GRADE and other methodological improvements including review of guidelines by the WHO Guideline Review Committee have added to WHO guidelines over more than two decades, we sought to explore how contrasting the GRADE EtD frameworks and the EML production process can shed light on challenges, and potentially propose adoption or adaptation of specific criteria that might be useful to address EML processes.

3. Methods

Overview

For developing this GRADE concept paper, we followed the process set out by the GRADE Working Group, outlining rigorous methods and policies for the approval of official GRADE articles [20, 21]. The development of GRADE papers is initiated by GRADE project group leads (in this case TP, LM, TK). The project group leads draft Terms of Reference (ToR) outlining the role of the group, group leads, GRADE Guidance Group liaison (in this case HJS), the specific objectives of the group, deliverables and timeline for the work. The approved GRADE for EMLs Terms of Reference are included as appendix 1.

Identification of key issues

We held an initial project group workshop hybrid – virtual and in-person - at the Krakow, Poland GRADE Working Group meeting on July 11, 2022 (approximately 30 participants). The purpose was to explore and ultimately establish a link between established GRADE criteria on the GRADE EtDs framework and the selection of essential medicines. The project group leads presented key conceptual considerations around Essential Medicines Lists to inform preliminary discussion and priority setting for future GRADE EML project group work. Initial priorities from the workshop were reviewed by project group leads and used to build a list of key conceptual issues to be included in a survey for the project group members. The purpose of the survey was to priority rank the items, while also seeking additional feedback from project group members including new issues and proposal for addressing these issues (see box 1 and appendix 2 for the survey).

Key deliverables from the initial project group meeting on July 11, 2022 are shown in box 1 below.

Box 1. Key deliverables from the July 11, 2022 meeting regarding the relation between EMLs and GRADE guidelines

- How to ensure that comparative cost-effectiveness is taken into account on WHO EML given WHO is not usually a funder of essential medicines & affordability differs by setting?;
- How to approach prioritization work up front for evidence synthesis for key disease areas/public health needs to inform which medicines should go onto EMLs?;
- How do guideline groups more effectively think about the barriers to availability of and access to essential medicines and what to do about them, so that their guidelines are more useful to EMLs?;
- How can we better engage/involve EMLs early on, perhaps consider the role shared participants/committee members?;
- How advocacy for medicine availability levers such as tiered pricing or voluntary/compulsory licensing agreements, to improve affordability and availability, can be advanced through guidelines and EMLs;
- Explore opportunities to map all guideline recommendations to EML medicines;
- Are guideline groups adequately considering removing redundant or problematic medicines (e.g. Antibiotics in context of resistance)?

We then held a series of online project group meeting which we recorded and summarized in meeting minutes that are available to project group members. Project group meetings included presentations of key conceptual issues including the EtD framework for EML applications (TP), the "chicken and the egg" issue of cost considerations for EMLs (FN) and what evidence should be required for EMLs to consider "me-too medicines" (structurally very similar medicines) using cancer as a case study (DT). Appendix 2 shows the results of the prioritization survey conducted to assess the importance and experience in relation to each preliminary challenge identified (see box 1) the characteristics of respondents to our initial survey and the results of prioritization and review of expertise are included in appendix 2 table 1 and the rating of importance and experience is provided in appendix 2 table 2.

Case studies

We prepared and reviewed relevant key case studies (boxes 2 – 4). The key case studies that we identified included: 1) two applications to the 2021 WHO EML – insulin analogues and anti-PD1 inhibitors for non-small cell lung cancer, 2) the linkage between guidelines and the national EML in South Africa, and 3) a Multiple Sclerosis International Federation guideline effort developed with the expressed purpose of informing a WHO EML application for the 2023 meeting of the Expert Committee. We iteratively discussed these examples to refine the key conceptual issues, and solutions proposed for them.

Box 2. Multiple Sclerosis International Federation (MSIF) Guidelines and 2023 EML Application [22-24]

The MSIF submitted a 2019 application to the WHO EML for 3 medicines to treat multiple sclerosis (MS) with support from various stakeholders. The application was rejected, and feedback was provided by the expert committee that a comprehensive assessment of all on- and off-label treatments for MS through a guideline process and subsequent EML application would strengthen the chance of future applications being successful.

Therefore, MSIF worked with Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System group and the MacGRADE Centre to develop two linked guidelines informed by Cochrane Systematic Reviews and following the GRADE methods for guideline development.

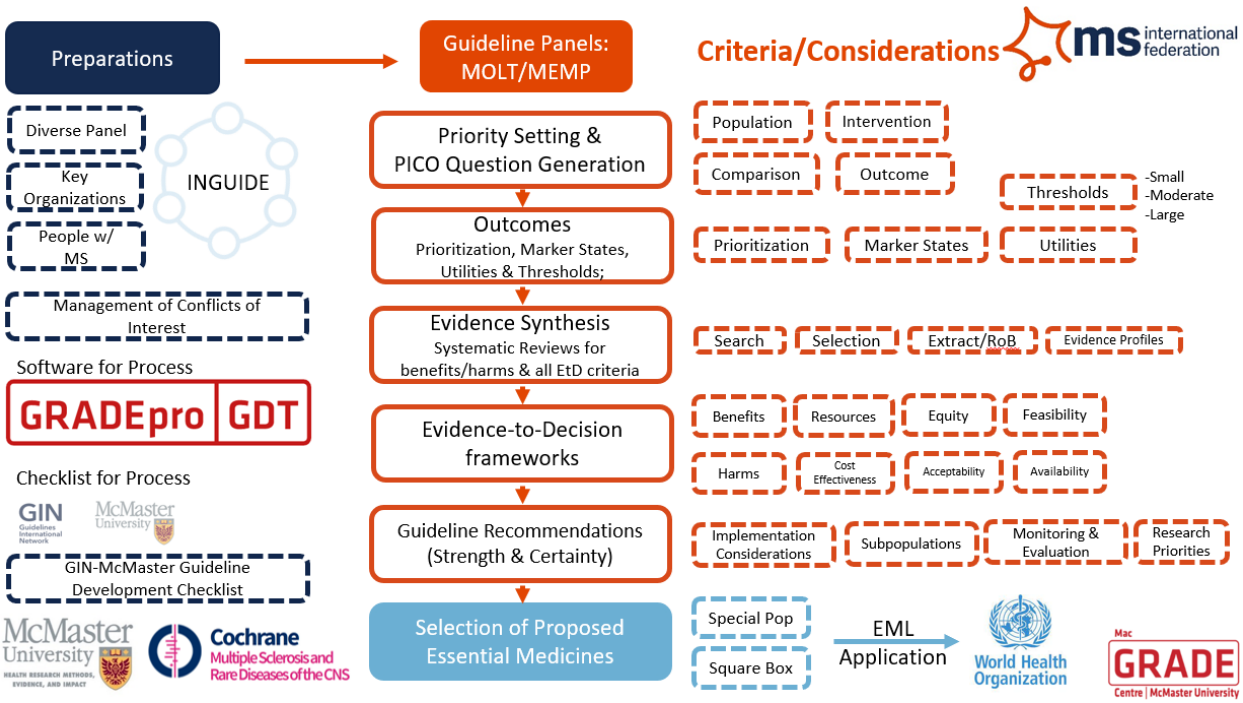
The methods used by MS Off Label Treatment panel (MOLT) and MS Essential Medicines panel (MEMP) to develop global guidelines for low-resource settings and inform EML application has been described in the publication Multiple Sclerosis International Federation guideline methodology for off-label treatments for multiple sclerosis [22].

The key features of the guideline included:
(a) Protocols, evidence reviews and final recommendations in peer-reviewed publications.
(b) An international multi-disciplinary panel with members who underwent detailed COI assessment and management in accordance with the GIN principles [25].
(c) Cochrane-led systematic evidence collection, synthesis and assessment using GRADE methodology [26].

(d) Systematic and transparent judgments made by the panel using EtD frameworks [27], standardized terminology for clarity [28] multiple-intervention comparison [29].
(e) Consultation with key stakeholders [22].
(e) Peer-reviewed publications of systematic reviews and guidelines informing this EML application.

Notably, building on previous work this guideline incorporated consideration of availability into the EtD [30]. This included extracting availability information from the systematic review on each EtD criteria, reviewing existing medicines on national EMLs, and assessing MS treatment availability data from the MSIF Atlas of MS treatments [31, 32].

Figure 1. Methods for the linkage between MOLT/MEMP guidelines and an EML application for the treatment of multiple sclerosis.



This structured process was found to develop a compelling application that will be submitted for consideration in 2023 by the Expert Committee.

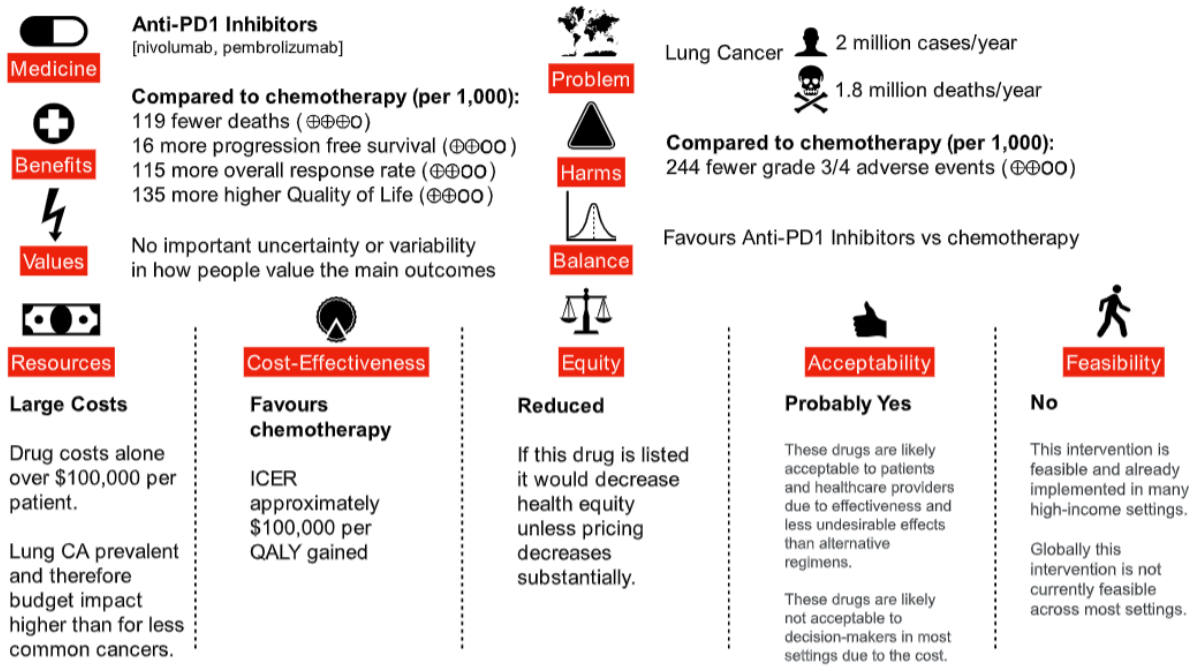
Box 3. Application to the 2021 WHO EML: Anti-PD1/anti-PD-L1 inhibitors for non-small cell lung cancer [33]

A 2021 WHO EML application supported by the European Society for Medical Oncology was considered and rejected by the Expert Committee on the Selection and Use of Essential Medicines. The application was based on a guideline that was developed in accordance to

ESMO methods [34]. These methods involve a review of literature and expert consensus process and do not utilize comprehensive GRADE methods.

To support the linkage between guidelines and EMLs a recent project created an EtD framework and 1-page visual abstract of decision criteria as adjunctive tools to support the consideration of EML applications by EML committees and conducted user-experience testing [19].

Figure 2. 1-page visual abstract of EtD framework decision-criteria.



In the creation of these tools, an examination of reviews was undertaken to identify evidence to inform the breadth of decision criteria in GRADE EtDs (benefits, harms, certainty, patients' values, balance of effects, resources required, cost-effectiveness, equity, feasibility, acceptability and availability).

In this process a Cochrane Review on precisely the same PICO question as the original application was identified that was published in December 2020, precisely the same month as when the EML application from ESMO was submitted to WHO. This example shows that a lack of coordination with other stakeholders engaged in evidence synthesis can result in decreased quality, duplication of work, public confusion and wastage of limited research resources (e.g., systematic reviewers, guideline developers, health technology assessment, essential medicine lists etc.).

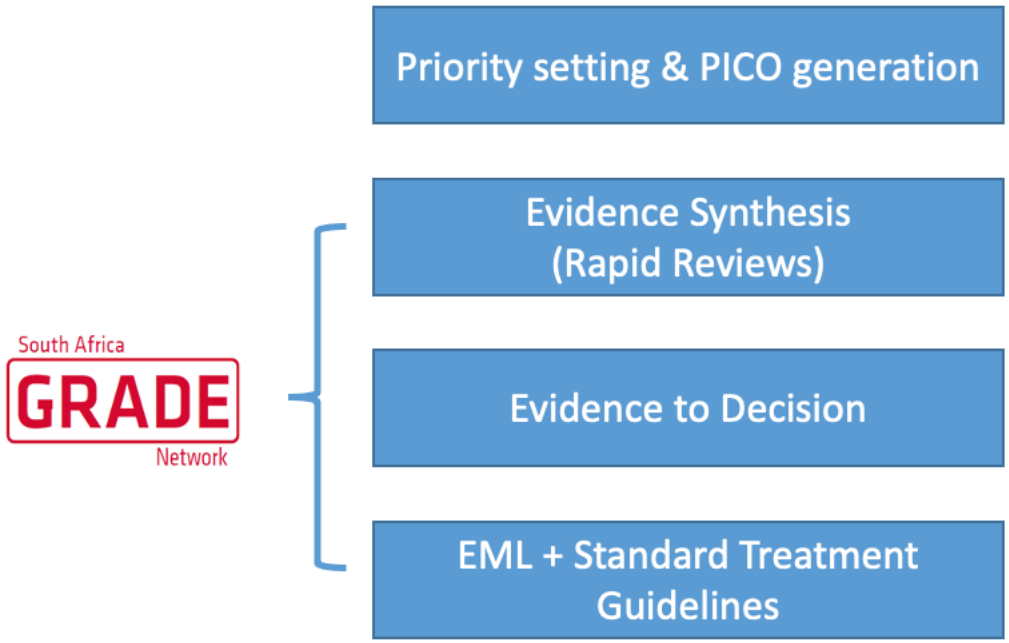
Box 4. The Standard Treatment Guidelines and Essential Medicines List for South Africa [25]

The South African EML combines both listing of medicines and clinical practice guidelines (CPG) that informs rational use of recommended medicines for primary and secondary level of care. Since 2008 when new medicines are added or reviewed for the EML this is accompanied by a linked guideline development process. The process has strengthened with grading of evidence evolving from SORT [26] to GRADE and from April 2020, fifty-six medicines on the South African Treatment Guidelines and EML were assessed using the GRADE approach and the Evidence to Decision Framework, underpinned by efficient rapid reviews to inform rational prescribing of essential medicines. Technical EML Committees are supported by the SA-GRADE Network, to conduct reviews utilizing Cochrane SR methods with adaptation/adolopment mechanisms using a systematic step-wise approach, reviewing high quality, up-to-date and relevant CPGs, SRs of RCTs, RCTs and then followed by observational studies, as appropriate.

The simultaneous review of the EML and respective guidelines came about due to resource constraints for evidence synthesis, but has been found to be a superior model to connect guidelines and EMLs, that could be considered elsewhere. Furthermore, the alignment between EMLs and STGs enables implementation of the EML through more efficient procurement practices using the tender system [27].

This connection, which involves a combined EML and CPG group, allows for efficient review and synthesis of evidence once and a close connection between both processes that are often disparate in other countries.

Figure 2. Scope and Process for South African Guidelines and EML.



Concept article preparation and approval

The draft concept paper was sent to the project group and feedback was incorporated before presentation to members of the entire GRADE Working Group who attended its virtual meeting on November 10, 2022 (by TP to approximately 115 attendees). Following that meeting, feedback from the GWG was incorporated to develop the final draft concept paper.

Results

We identify six conceptual issues, and corresponding examples or evidence and solutions or insights. This paper serves as preliminary findings that may be further developed into guidance as additional engagement with key stakeholders continues. Table 1 shows the final list of key

conceptual issues, a description of links to examples, and proposed solutions for further exploration and implementation.

Table 1. Key Conceptual Issues for EMLs, Examples/Evidence and Proposed Solutions for Further Exploration

Key Conceptual Issues	Examples/Evidence	Proposed Solutions/Insights
1. How can the connection between systematic reviews, guidelines and EML applications be improved to improve use of shared evidence syntheses and accelerate access to essential medicines?	The MSIF guidelines (see box 1, MOLT & MEMP) process was conceived to link to an EML application effectively and efficiently. This resulted in rigorous and trustworthy guidelines and an application to the WHO EML.	1.1 Governance structures tailored to countries (e.g., legislative/legal frameworks) for connecting health decision processes at the country-level should be creating aligning health technology assessments, guidelines, coverage/reimbursement lists and EMLs [15]. 1.2 Shared committee members between guideline and EML committees could provide direct linkage [35]. 1.5 An alignment of PICO question priorities between guidelines and EMLs, should be undertaken together on a macro-level (disease categories) and micro (specific medicines) level. 1.4 Requesting that guideline groups consider whether medicines they recommend are essential, and if so prompt linkage to an application to the WHO or national EML. This could be an implementation consideration in established GRADE EtDs (e.g. a section that asks is this medicine current on an EML? If not does the panel feel it should be added through an application?). A link in the EtD to essentialmeds.org or recommendation maps (covid19.recmap.org) could facilitate checking by guideline panels.[36] 1.5 Request EML applicants review and consider whether medicines they are applying for are supported by health guidelines and for which indications. 1.6 Develop a software solution or streamlined application approach to connect trustworthy guidelines and EML applications (e.g. API (Application Programming Interface) to export evidence from guideline to EML application).

		1.7 Use of GRADE methods (e.g,. certainty assessment, evidence profiles & evidence-to-decision frameworks) in guidelines informing EMLs or applications to the EML could standardize methods that might improve the trustworthiness of EMLs. 1.8 If the methodological requirements of EML applications are clarified (e.g., requiring a link to systematic review or guideline) an appropriate quality appraisal tool could be used to assess the underlying evidence and quality of applications (e.g. AMSTAR II, ROBIS, AGREE II). This would support choosing the most up-to-date, relevant and credible sources of evidence in the event of multiple eligible systematic reviews or guidelines. 1.9 Established processes to manage conflicts of interest in guidelines could also be used for the management in EML committees (GIN principles [25]). Feedback from members of the committees using tools such as PANELVIEW may be considered. 1.10 When a guideline (in particular a WHO guideline) makes a recommendation against a medicine that has historically been on essential medicines list for that indication (e.g. evolving evidence demonstrates greater harm than benefit) they should apply to remove that medicine from the EML to ensure coordination between guidelines and EMLs.
2. What should the certainty of evidence, strength of recommendation, and key decision criteria (e.g. cost-effectiveness, equity etc.) be for a medicine assessed by a guideline to be considered essential?	Me-too medicines for cancer often face large regulatory hurdles but could provide more benefits across other EtD criteria such as cost and availability.	2.1 GRADE certainty assessments could be completed for medicines considered by the EML if not available from the source systematic reviews. Similar to GRADE language for informative statements in systematic reviews and guidelines based on the certainty and size of the effect may be useful to communicating EML medicines [37]. 2.2 Absolute effects should be considered by EML applicants and committees, as these take into consideration baseline risk compared to relative effects when making judgements around benefits and harms. Where baseline risk differs substantially, EML committees

		should considering using contextually appropriate baseline risk to calculate absolute effects. 2.3 Clarity on which outcomes are most important to EML committees could be sought. Should only critical outcomes such as mortality, quality of life, inform decisions for EML committees? 2.4 Medicines may be essential even if the evidence on their benefits and harms is low or very low certainty, or a guideline issues a conditional recommendation. This is a fine balance, because one may not want extensive listing/de-listing of medicines with low or very-low certainty evidence, where the evidence base may evolve. 2.5 The established considerations for strong recommendations with low certainty of evidence may be informative for consideration of listing essential medicines that have low or very low evidence [38]: -life threatening situation -uncertain benefit, certain harm -potential equivalence of benefits/harms, clear cost difference -high certainty similar benefits, uncertain harms/cost Unique to the EML, additional criteria may include medicines available to treat a condition with a significant burden of disease or where an important gap in treatment availability exists within the EML. 2.6 EMLs could consider the provisional (or conditional) listing of an essential medicine that has low or very low certainty and recommend additional research. 2.7 Medicines, conditionally recommended by guidelines may be considered for the EML when: -conditional because of variability in values/preferences or cost (e.g. HPV vaccine where values are important);

		- conditional based on baseline risk of a key outcome/ burden of disease (e.g., might not be a priority issue for the country [EtD domain 1]). 2.8 Building off recent published work on the decision-criteria for cancer medicines on the WHO EML, clarity should be sought on outcomes important to EMLs and whether disease category specific criteria (such as those provided for cancer) are needed or if the same criteria and thresholds for benefit/harms should apply to all medicines considered [39].
3. Should availability/cost (price) of a medicine be considered in whether a medicine should be listed on an EML, or is it in fact an objective of EMLs?	In developing the MSIF MOLT/MEMP guidelines and linked EML application, the guideline group struggled with whether to consider the present state on issues such as availability/cost of medicine in judgements, or whether they should consider a future state where medicines are listed on the EML. This is because the group felt that listing on an EML could help decrease cost and increase availability and should therefore not be a pre-condition to being considered essential.	3.1 Further explore when cost (price) should be a factor in relation to the benefits/harms balance of a medicine. In some settings this may involve a cost-effectiveness threshold or other willingness to pay threshold (e.g., linked to GDP as presented previously by WHO). However, EMLs consider that cost is a fluid and often industry-driven concept. Essential medicines should be made more affordable as much as possible to improve their appropriate use. One such piece of evidence that could inform EML decisions is the range of price negotiated in different countries. This data is frequently not available due to non-disclosure agreements, but where there is variability in price due to negotiation consideration the lowest price ranges should be considered as feasible in many settings. 3.2 Have EML committees clarify whether cost is in fact a consideration in relation to the WHO Executive Board resolution that states it should not be a reason for not listing a medicine. This stands in contrast to reimbursement lists or coverage decisions, which may have to consider budget impact and affordability of medicines in a country. We discussed that cost as a criterion for EML listing can be like the 'which came first the chicken and the egg' situation, because listing on an EML can lead to strategies that may decrease costs (including market concentration, bulk purchasing, or voluntary patent agreements).

		3.3 Further define how rare diseases should be treated by the EML. Budget impact should inform the assessment of inclusion for diseases, which would address rare diseases that may have treatments that could still be considered essential medicines. Guidance on how to use GRADE in rare diseases can be utilized to inform these discussions [40-42]. Examples of guidelines developed using the GRADE methodology and addressing rare disease, rigorously considering issues around cost and accessibility can be usefully reviewed [43-46].
4. What approach can be taken to transparently identify therapeutic alternatives (square box indications) for medicines, and how should clinical equivalency be assessed by EML applicants?	In the MSIF MEMP panel (see box 1) a rigorous guideline process included a network meta-analysis of all disease modifying treatments for MS. This included the setting of thresholds based on health state utility values to inform judgements on trivial/small/moderate/large benefits and harms. After recommending medicines in order of their preference, consideration of children, pregnant and breastfeeding people was undertaken to inform the final selection of medicines to be proposed for the 2023 WHO essential medicine list application.	4.1 In determining medicines for EMLs, consider medicine groups *a priori* that should be considered as the same therapeutic class and could later be proposed for "square box" symbol listing on the WHO EML. 4.2 In addressing gaps in an essential medicine list, ideally use evidence synthesized by a systematic review and network meta-analysis, or a scoping review, to have a quantitative assessment of the benefits and harms. This may be challenged if there are not randomized control trials for the medicines reviewed. 4.3 Use guidance, ideally fully contextualized, including decision thresholds, to support the ranking of medicines to select those that are most essential [47]. 4.4 Consider the range of special populations (e.g., children, pregnant, breastfeeding) that should be covered by selected final medicines that will be proposed to inclusion in an EML. 4.5 Consider established evidence on therapeutic equivalence of medicines (e.g., FDA Orange Book). 4.6 Make use of conceptual guidance on operationalizing biological plausibility in GRADE evidence certainty assessments to inform

		certainty assessments for me-too medicines being considered by EMLs [48].
5. What can be done to support contextualization of the WHO EML to the National level?	The South Africa EML considers equity in its EtD framework. Through the use of EtD frameworks by the WHO EML this could make synthesis of evidence for new medicines considered by the South Africa EML, and other national EMLs, more efficient and effective.	5.1 A contextualization approach that transparently notes and shares the decision criteria considered for the acceptance or rejection of an essential medicine from the EML to national EMLs, such as GRADE adolopment (or other contextualization tools) could support linking more efficiently to enable changing of criteria as applicable at a local level [49]. 5.2 The WHO EML could provide clear considerations in the form of national implementation considerations that could suggest reasons for countries to consider listing or not listing a newly considered medicine (e.g., epidemiology or problem priority) and suggestions on improving access. 5.3 Future stakeholder engagement work could explore opportunities to harmonize the policies and methods for national EMLs to improve transparency and evidence-based decisions and decrease inappropriate variability in NEMLs. 5.4 Guidance could explore the key local contextualization factors for national EML committees to consider (e.g., local acceptability of listing a medicine may be very important or adjustments in baseline risk of a critical outcome).
6. How should EML committees consider equity?	In the MSIF MOLT/MEMP guideline GRADE guidance on equity, and a systematic review of equity considerations, was used to inform the guideline recommendations and medicines selected for application to the WHO EML. The group considered both within country equity (e.g. medicines that required infusion may decrease equity in rural areas if it is not feasible) and	6.1 EML committees could explicitly include equity as a criterion considered and create a consistent approach for doing so. Currently, the WHO EML implicitly considers equity in many decisions but it is not a criteria outlined in the current procedure [19]. 6.2 EML committees could consider GRADE equity guidance to inform equity considerations by EML committees [50-53], this could include consideration of populations outlined by the PROGRESS-Plus and whether they would be positively or negatively impacted by listing a medicine on an EML.

	between countries (more expensive medicines may not be affordable in lower income countries and the impact would be negative on global equity). Decreased equity due to high price of medicines was thought of as a modifiable barrier, because the group felt equity could be improved through price reductions.	6.3 If equity is a EML criterion, or an assessment of it desired by guidelines linked to EMLs, clarity in instructions needed to focus review on within or between country equity issues, or both. 6.4 Equity in priorities of medicine applications, and guidelines or evidence synthesis work should be considered [54]. Efforts by WHO to facilitate globally equitable prioritization for evidence synthesis should be undertaken.

Discussion

We developed a GRADE concept article we describe potential solutions for the connection between EMLs at the global and national-level and health guidelines. The challenges focus on the following six domains and EtD criteria: 1. How to improve the connection between systematic reviews, guidelines and EML applications to accelerate access to essential medicines?; 2. What certainty of evidence and strength of recommendation based key decision criteria are essential for the EMLs?; 3. Should availability or cost of a medicine for listing in the EMLs?; 4. How to transparently identify square box indications for medicines, and how should equivalency be assessed by EML applicants?; 5. What is required to support contextualization of the WHO EML to the National level?; and 6. How should EML committees consider equity?. Utilization of our proposed concepts will help identify solutions for the challenges beyond the ones we have identified here.

Strength and Limitations

The strengths of this GRADE concept article include the rigorous and expert-engaging process for GRADE papers.[20] It also includes novel conceptual solutions to key issues related to the development of trustworthy essential medicine lists. The solutions we present advance an important area of research to contribute to better EMLs and ultimately improved access to medicines and universal health care. The key concepts explored in this paper were identified and informed by the project group and examples identified. A limitation, therefore, includes the potential for missing some stakeholders' perspectives. Participants were predominantly from

the WHO PAHO, EURO and AFRO regions, particularly given the importance and divergence of national decision in access to essential medicines. Therefore, further engagement of individuals from other global regions should be undertaken to review concepts and unique considerations from those settings before GRADE guidance can be developed. Furthermore, the GRADE for EML project group has expertise primarily in evidence synthesis. To further advance implementation particularly as it relates to reforming governance structures to improve process and alignment of EMLs and guidelines, involvement of appropriate policymakers and other stakeholders will be needed.

Implications for practice and policy

Many of our practical solutions can be easily and immediately implemented by guideline groups and EML committees. Organizations that sponsor EML committees, such as the WHO, could review suggestions herein, to consider policy and structural changes that may improve the rigour and trustworthiness of EMLs. Notably, these solutions include aligning guideline groups and EMLs, potentially considering shared participation to strengthen linkage, using explicit and shared criteria to make guideline recommendations and EML decisions, and using specific criteria when deciding to list essential medicines that have low or very low certainty evidence. We also provide recommendations to strengthen alignment between the WHO EML and NEMLs, which in part can be done through following principles of guideline contextualization through methods such as GRADE adolopment [15, 49].

Finally, we present a range of recommendations for health guidelines to consider EMLs in their planning and development. Future changes to EML decision criteria would therefore require Executive Board approval by WHO, and recommendations considered in this work, while they may apply to NEMLs as well would need to be taken under consideration by the Executive Board. These include the consideration of whether new applications for the addition or removal of medicines from EMLs should be made resulting from guideline recommendations. They are included utilizing similar rigorous and transparent processes, now familiar in guideline development, to support the preparation of EML applications.

Implications for research

Our work presents unanswered questions that should prompt future engagement with additional key stakeholders. These questions include exploration of medicine cost-implications and explicit strategies that could be facilitated by listing essential medicines on the WHO EML and NEMLs to decrease cost of medicines and improve availability (e.g., tiered pricing, voluntary licensing agreements, tender-based procurement practices and market concentration). A priority in relation to EMLs for the GWG will be to develop a structured and operationalized approach to linking decision criteria for the selection of essential medicines to health recommendations through a GRADE EML EtD. At a country level, further research to understand NEML decision-making process and methods of development across a range of country settings, notably those where inequitable access to medicines is most significant, and whether solutions proposed here have applicability across those settings.

Another area of research includes prioritization of medicines for consideration of inclusion on EMLs. WHO has historically prompted section reviews relating to disease classes. In the most recent relating to cancer medicines, methodological research and sharing has been very helpful [18]. Future research could address how to identify important gaps for diseases, or disease classes to prioritize future EML applications. WHO has created a searchable WHO EML and NEML database at essentialmeds.org [55]. An example of connecting health guideline recommendations to EMLs is through the eCOVID-19 recommendation map [36]. The availability of additional recommendation maps would improve this connection [56, 57]. Thus, this work fits with broader work to identify and advance synergy in a range of health decision-making paradigms, including guidelines and EMLs [15]. We plan to develop a GIN-McMaster checklist extension for considering EMLs in the guideline development process similar to the extensions for quality assurance and stakeholder engagement [58-61].

Conclusions

This GRADE concept article, based on involvement of key stakeholders from the guidelines and EMLs field, identified key conceptual issues and potential solutions to support the continued advancement of trustworthy EMLs. EMLs are an important prioritization tool, at the global and national level, that work to prioritize essential medicines to improve their availability and use to improve health in the context of universal health coverage. To advance health equity, gaps in availability of essential medicines should be addressed within and between countries. Our concepts and solutions help taking first steps to achieving this. When additional examples are

available, a fully operationalized GRADE EML EtD framework may become reality and we hope will be helpful to improving the trustworthiness of EMLs.

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Chapter 4: Appendix 1: GRADE for EMLs Project Group Terms of Reference

GRADE project interest group

GRADE project group on Essential Medicine Lists

Terms of Reference

Drafted by: Thomas Piggott Revised by: Tamara Kredo, Lorenzo Moja, Benedikt Huttner, Holger Schünemann	May 30th, 2022

Name of the project group:

GRADE project group on Essential Medicine Lists

Role of the project group

Essential Medicine Lists (EMLs) are critical for prioritizing medicines around the world and ensuring people have access to them. Essential medicines meet the priority health care needs of the population, and are intended to be available at all times within functioning health systems in adequate amounts, dosage forms, and quality assurance at an affordable price. The World Health Organization (WHO) Model List of Essential Medicines (MLEM) has prioritized

medicines since 1977 and over 137 countries around the world also have national EMLs, which inform coverage decisions and ultimately availability of these medicines to those needing them. Prescribing of medicines that are deemed essential should be grounded and prescribed based on reliable evidence and, when possible, in close alignment with clinical practice guidelines. However, the relationship between essential medicines and guideline recommendations is not always linear. There are cases in which guideline recommendations are developed first and the same evidence base is used to build the case to include a medicine in the national EML. There are other instances in which a medicine becomes essential while there are not yet guideline recommendations available to guide its use in clinical practice. The opposite is when a guideline recommends a medicine but the same medicine is not listed as an essential medicine as it has never been evaluated. In rare cases guideline and essential medicines list might diverge. A paradigmatic case is when a guideline issues a weak recommendation, and the same medicine is rejected as an essential medicine. Weak recommendations might originate legitimate divergences between guidelines and essential medicines lists. However, if a medicine is recommended as part of a strong recommendation, it is more difficult, at least theoretically, to justify a rejection as essential medicine. All these above mentioned scenarios show the complex interplay between two key tools designed to support best care practice.

Despite different approaches for development of guidelines, HTAs, EMLs – the fundamental methods do align in many of the domains that inform decisions/ recommendations. To avoid duplication of efforts, ideally the evidence that informs various health decision products (guidelines, HTAs, EMLs etc) should be based on common methods and rigorous underlying assessment of the research evidence in a format that can be shared (see Schünemann 2022

Lancet Public Health). GRADE has supported Evidence-to-Decision framework develop for a broad range of health decisions (clinical, diagnostic test, public health, coverage decisions etc.). The EtDs support a wide range of health decision-making, and it is believed that the transparency in criteria could support essential medicine selection. This project group will look at issues specific to EMLs as it pertains to not only EtDs but is aimed at exploring the dynamics between guidelines and coverage decisions, in an effort to enhance synergies, improving the trustworthiness and transparency of these complementary tools.

Specific objectives

Explore relationship of decision criteria of EML applications to GRADE guidance domains, emphasizing synergistic approaches (e.g. systematic review as foundation evidence supporting the decision making process).

Develop guidance on using methods that reinforce a coordinated approach which encompasses both guidelines and procurement/coverage decisions using GRADE EtDs. Guidance might extend to other prioritarization tools such as the list of essential diagnostics.

Assess what considerations apply primarily to EML applications and what EtD modifications may be required (e.g. addressing availability of medicines, patent and licensing issues, square box and pharmacological equivalency).

Address how applications related to essential medicines can be improved in terms of transparency, comprehensiveness and reporting using GRADE principles.

What do we know about methods for adapting global EML to national settings using GRADE principles?

Deliverables

GRADE Concept or Guidance Paper on GRADE for EMLs.

Timeline

Year 1 (ending 2022):

- Identify key stakeholders and conduct small group session at the July 2022 GRADE meeting in Krakow.
- Finalize and publish GRADE paper #1 on GRADE for Essential Medicines.

Year 2 (2023):

To be determined.

Chapter 4: Appendix 2: Project Group Priority and Expertise Survey

A prioritization survey was conducted with participants in the GRADE for EMLs project group. n=13 participants

Appendix 2. Table 1. Respondents' characteristics of the prioritization survey		
Characteristic	**Description**	**Number of Respondents (%)**
Area(s) of Expertise	Systematic Review Expert	9 (69%)
	Health Research Methodologist	6 (46%)
	EML Committee Member/Technical Expert	5 (38%)
	Guideline Developer	4 (31%)
	Health Policy Expert	2 (15%)
	Health Technology Assessment	1 (8%)
Experience Submitting WHO EML Application(s)	Yes	7 (54%)
	No	6 (46%)
Experience Submitting National EML Application(s)	Yes	1 (8%)
	No	12 (92%)
Familiarity with Guideline Development	Median Score, 5-point Likert Scale (Range)	4 (3-5)
Familiarity with EML Development	Median Score, 5-point Likert Scale (Range)	4 (2-5)

Appendix 2. Table 2. Prioritization and Identification of Expertise of Preliminary Conceptual Issues		
Key Issue	**Median Priority, 5-point Likert scale (range)**	**Median Expertise, 5-point Likert scale (range)**
1. How can the connection between systematic reviews, guidelines and EML applications be improved to improve quality and accelerate access?	5 (2-5)	3 (3-5)
2. What should the certainty of evidence, strength of recommendation, and key decision criteria (e.g. cost-effectiveness, equity etc.) be for a medicine to be considered essential? (*exception historical use of medicines that will not get new evidence; when there is futility)	4 (4-5)	4 (2-5)

3. Should availability of a medicine be considered in whether a medicine should be listed on an EML, or is it an objective of EMLs?	3 (1-5)	2 (1-4)
4. What should be considered in determining a pathway to access or implementation plan for essential medicines (e.g. voluntary licensing agreements, market concentration etc)?	3 (1-5)	2 (1-4)
5. What approach can be taken to transparently identify square box indications (class effects) for medicines, and how should equivalency be assessed by EML applicants?	4 (2-5)	2 (1-4)
6. What can be done to support contextualization of the WHO EML to the National level?	4 (3-5)	2 (1-5)
7. How should EML committees consider equity? (framework, e.g. PROGRESS-Plus)	4 (3-5)	2 (1-3)
8. How can network meta-analysis and multiple intervention comparison be used to synthesize evidence and support the selection of the most effective essential medicines in a disease area?	4 (2-5)	3 (1-5)

Chapter 5: Conclusions

Overview

In this thesis, I have explored the criteria and processes to develop EMLs and their connection with guidelines. I have user-tested an EtD framework and visual abstract to facilitate the connection of EMLs and guidelines and improve the integration of evidence into EML decisions. I have additionally provided guidance on the connection between guidelines and EMLs through a technical and methodological expert-stakeholder driven GRADE concept paper.

The overarching connection of this work is strengthening the synergy between EMLs and guidelines. This has been part of a broader effort to coordinate and find opportunities to align more broad health decision paradigms including systematic reviews, health technology assessments, guidelines, quality improvement, coverage decisions, EMLs, and evidence-informed policy making [17].

Implications for Policy and Practice

This research has taken an applied approach to the development of tools, including an EtD and visual abstracts, and GRADE Working Group guidance, to create actionable opportunities for the improvement of applications and decision-making by the WHO EML.

As articulated in chapter 2, it would be ideal to create a global “evidence pipeline” to inform the generation and application of a shared evidence base for decisions by both guideline groups and EMLs. While priorities may differ, improved coordination and communication could lead to

the use of the same underlying evidence synthesized through systematic reviews. Doing this in practice will take several key changes, with implications for policy: 1) awareness by EML and guideline producers of each other's processes and priorities, 2) alignment in governance structures globally and nationally, and 3) appropriate resources committed by WHO and other institutions to successfully advance this work, and 4) ensuring appropriate connection to other critical components of medicine access.

Awareness and education of guideline and EML producers is important to ensure there is an understanding of each other's health decision-making paradigm processes, which, in turn, supports potential collaboration. Many individuals with expertise in either EMLs or guidelines, whom I interviewed through the course of my thesis, quite reasonably did not have exposure and clarity on the other's decision-criteria and processes. Education, perhaps as part of training for new EML or guideline committee members, and the technical staff supporting these endeavours, is important to improve active awareness of guidelines/EMLs by the other.

Secondly, alignment of governance structures is important to support synergies and remove barriers to collaboration. This may involve an overarching legal framework that we described and encompasses roles and processes among all health decision paradigms [17]. The nature of the governance structure would be quite context dependent. At a global level re-examining the executive board resolution on selecting essential medicines would be sufficient possibly allow clarification of criteria and processes to bring guidelines and EMLs more closely aligned. For example, there could be required consideration or funding to support application to the EML for all relevant guideline recommendations.

There will be contextual variation in applying this work at national levels. In unitary nations a national structure may advance this synergy; however, in federated countries, such as Canada, this would need to involve sub-national governments such as provinces with whom much of the responsibility for health decision-making may reside. The potential benefits to coordination include reducing the duplication and wastage of evidence synthesis efforts, and correspondingly the capacity to address more evidence-synthesis priorities. Exploration of an evidence pipeline by WHO and at country-levels, as articulated in chapter 2, would support clarity on connections between EMLs and guidelines, and other health decision-making paradigms.

Thirdly, while the work presented in this thesis is focused on processes for decisions for EMLs and guidelines, an important related piece of work is the assessment and improvement of access to essential medicines. This tremendous work necessitates trustworthy EMLs as a starting point, but recognizes listing medicines alone is not enough to ensure access. Implementation through various mechanisms, and quality improvement and monitoring on the access this enables to essential medicines is critical for people who need these medicines to actually receive them. The Lancet Commission on Essential Medicine Policies proposed numerous policy mechanisms to decrease price and improve access to essential medicines, these included: procurement interventions, pro-generic policies, pricing interventions such as voluntary licensing agreements, quality use of medicines, trade-related intellectual property flexibility [4]. The Lancet Commission also emphasized the need to improve data sources on medicine access of essential medicines to support monitoring and tracking improvements.

Fourthly, improving the rationale selection of essential medicines and the connection to guidelines alone does not bridge the inequitable access to essential medicines globally. Ensuring appropriate health system structures, financing mechanisms, and ultimately appropriate availability and prescribing, and feeding this back to inform quality improvement are also critical considerations that should be further connected. These aspects will require engagement of experts in these domains such as health system and implementation experts.

While the EML has been impactful in supporting access, there are still important improvements to enhance the trustworthiness of EMLs through ensuring the best processes and decisions on essential medicines.

Implications for Research

Several overarching research priorities emerge beyond those articulated in the preceding chapters. Firstly, while chapter 4 addresses implementation of guidance on connecting guidelines to EMLs through case studies in the South Africa EML and the MSIF guidelines connected to an EML application, further case studies and evaluation of the proposed guidance is needed. In particular, evaluation of the recommended processes with the WHO Expert Committee and with national EML committees is needed to assess how committee members perceive applications linked to guidelines, and how the processes proposed herein impact EML decisions.

We have described the significant divergence of EMLs at a national-level globally [20]. Monitoring the evolution of national EMLs over time, and through enhanced support for

trustworthy linkage to the WHO EML and guidelines is needed to improve alignment of national EMLs while still supporting appropriate contextualization. The GRADE concepts, presented through chapter 4 should be further evaluated within both GRADE guideline and EML communities to ensure clarity, feasibility, and utility in implementation.

This thesis presents, as it's foci, the opportunity for collaboration between EMLs and guidelines. As part of future work, quantifying the efficiencies and improvements gained through closer collaboration and reducing duplication of work is important to assess impact and implications for connecting other health-decision paradigms.

Ultimately, as discussed, an EML is only as good as its implementation. As articulated in the Lancet Commission, data on access for essential medicines at a national level is an important priority to tracking and improving access [4]. This should be both facilitated by WHO through pushing quality indicators and mechanisms for reporting, and through pulling important access information from available sources, as is effectively done for data on other subjects, notably reporting of important communicable disease epidemiology and treatment outcomes (e.g., TB, HIV).

There are a number of future research topics that have been identified through this work that should be explored through empirical means. While we have explored the connection between guidelines and EMLs in theory and through real case studies, the nature and number of medicines on EMLs that are currently supported by underlying guidance is not known. This, as well as a review of trustworthy WHO guidance that has resulted in the recommendation of medicines that have not ended up on EMLs, should be empirically assessed to better

understand the current state of the connection, and medicine/disease areas where the connection is particularly effective or absent. Finally, the connection between EMLs and guidelines should not proceed in a vacuum. An understanding of the connection of guidelines and EMLs and other health decision paradigms is critical to advancing the field of health evidence as a whole.

Conclusions

This thesis has explored EMLs, their process and basis in evidence, and connections with guidelines. Improved coordination between EMLs and guidelines is needed to support more effective health decisions, however, this alone will not drive improvements in universal health coverage and health outcomes. Significant work is required to improve implementation and monitoring of essential medicines so that access is more equitable globally and so that people, no matter where they reside, can achieve the health improvements afforded by these medicines.

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