Estonian Handbook for Guidelines Development

2016

Acronyms and Terms

A full glossary of terms and their definitions may be found at the end of this handbook.

ROBIS Tool to assess risk of bias in systematic reviews

AGREE Appraisal of Guidelines Research and Evaluation instrument

AHRQ Agency for Healthcare Research and Quality (U.S. Department of Health and Human Services)

CADTH Canadian Agency for Drugs and Technologies in Health

COI Conflict of interest

DOI Declaration of interest

EHIF Estonian Health Insurance Fund

GRADE Grading of Recommendations Assessment, Development and Evaluation

GAB Guideline Advisory Board

GP Guideline Panel

ICER Incremental cost-effectiveness ratio

MeSH Medical Subject Headings (U.S. National Library of Medicine)

NICE National Institute for Health and Clinical Excellence in the United Kingdom

PICO Patient/Population-Intervention-Comparison-Outcome

QALY Quality-adjusted life years

WHO World Health Organization

Foreword

Context for guideline development in Estonia

Clinical practice guidelines are generally accepted as an important tool for improving the quality of clinical care provided by health professionals, as well providing guidance to ensure the quality use of medicines and health technologies. Beginning in 2003 and continuing through 2009, several institutions and professional bodies in Estonia, having the quality of the health services as their goal, have supported or carried out the development of national guidelines.

In 2015, a comprehensive assessment of the situation was carried out by the World Health Organization (WHO), EHIF, the Medical Faculty at the University of Tartu, and national and international experts in an effort to assess guideline development in Estonia from 2011 onwards. From 2011-2015 were developed all together 7 National Clinical Guidelines. The assessment process resulted with recommendations, how to improve the clinical guideline development process. It resulted in a new, second version of The Estonian Handbook for Clinical Guidelines Development.

An updated process, described in a reviewed handbook set up by the Medical Faculty at the University of Tartu and by EHIF, and endorsed by the Ministry of Social Affairs, supports a consistent approach to guideline development. The updated version of The Estonian Handbook for Clinical Guidelines Development contains the same principles as previous version with improvements recommended by WHO experts. The handbook has been complemented with two additional chapters: one describes the development of clinical pathways, the second new chapter describes the development of patient guideline, which is intended to complement the approved clinical guideline.

This handbook is intended to bring together the experience gathered thus far and the current internationally accepted methods for developing guidelines. It intends to cover all aspects of guideline development, starting with assessing the need for guidelines and finishing with the distribution, implementation, and updating of guidelines. The Handbook is valid from the date of acceptance of GAB.

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Description of guidelines

The World Health Organization defines guidelines as…

"….systematically developed evidence-based statements which assist providers, recipients and other stakeholders to make informed decisions about appropriate health interventions. Health interventions are defined broadly to include not only clinical procedures but also public health actions. Guidelines are formal advisory statements which should be robust enough to meet the unique circumstances and constraints of the specific situation to which they are being applied."[1]

Well-developed and high quality guidelines provide the basis for promoting quality of care in a health system. The need for country-specific guidelines is envisaged in most clinical specialities. If the guidelines are based on evidence, accepted by local health professionals, and linked with performance indicators, implementation strategies they can lead to improved quality of care, and health outcomes. Local costs and community values, as well as the inclusion of clinical evidence, need to be considered during the development of and approval process for guidelines. The use of international resources for clinical evidence synthesis is encouraged.

The main difference between a guideline and a textbook is, a guideline concentrates on actions for diagnosis and treatment of patients, while a textbook provides a comprehensive description of all aspects related to a particular disease.

Sometimes, strategies other than guidelines are more appropriate and effective to improve quality of patient care, such as:

- regulatory / legal remedies;
- rewards / penalties;
- system strategies (e.g., referral mechanisms);
- peer review, audit, and feedback;
- training / instructions.

Before starting the process of guideline development, it is important to consider what the objectives are for the guideline and whether a guideline is really the best approach to reach the stated objectives. It is likely that guideline development in Estonia will be concentrated on the important health conditions in the country (Chapter II-1: Topic proposal and selection).

The process for one guideline development takes approximately 2-3 years and each completed guidelines will be reviewed after five years. The process for guideline development has to be fully transparent, carefully considered, and created in close cooperation with all stakeholders. The process does not end with

[1] Global Programme on Evidence for Health Policy. Guidelines for WHO Guidelines. EIP/GPE/EQC/2003.1. Geneva: World Health Organization; 2003.

approval of the guideline; further action is needed to ensure that the guideline is implemented not only in practice, but that it's stated objectives are achieved.

A need for a guideline can be identified by any organization (i.e. professional society, patient group, academic institution, EHIF etc). The guideline initiator should submit a topic proposal (see Chapter II-1: Topic proposal and selection) and a draft scope (Chapter II-2: The scope of the guideline) to the Guideline Advisory Board (GAB). GAB is an advisory group whose tasks include the annual selection of potential guidelines for development out of proposed topics, and acceptance of the final guideline for approval (Chapter I: Guideline development groups).

Together with developing recommendations for Clinical guideline started with completion of the Guideline for Patients by the guideline's secretariat. The aim of such guideline is to provide patents with relevant health issue and the general public with state-of-the-art treatment information in easy-to-understand language.

Third part of guideline is the Clinical Pathway which provides for health specialists, stakeholders agreement how patient should be handled between different stages of health care system in Estonia.

Development of a guideline is overseen by a multidisciplinary Guidelines Panel in close collaboration with the Guidelines Secretariat (Chapter I-3). The Secretariat offers technical support to the Panel. The Panel for each guideline is selected and appointed by the GAB, while the members of the Secretariat are identified in co-operation with the Faculty of Medicine at the University of Tartu and the EHIF.

The funder is concluding agreements for fixing of working relationship with the team of clinical guideline, confirmed by GAB, with the purpose to agree the roles, main tasks and compensation of performed costs of Panel and Secretariat members.

After the confirmation of the Panel of clinical guideline in GAB, the funder of the guideline will contact the employer of every Panel member and inform him about the nomination of expert, his/her role and expected time expenditure in the process of development of clinical guideline. For the avoiding of conflict of interests and ensuring of neutrality of recommendations the contribution of Panel members will not be financed additionally. The agreements concluded with the Secretariat members will establish working hourly wages and the format of reporting about the working activities. The other costs of funder of clinical guideline will cover the costs for transportation and training of both Panel and Secretariat members.

The Guidelines Panel presents the final scope of the guideline to the GAB for approval. After completion of the guideline development process, the GAB has responsibility for approving the guidelines together with implementation of the plan. For final approval, the GAB has to confirm that the guideline methodology and development processes were followed by the guideline developer.

The development of guidelines may be financed by EHIF or by other independent organisations or institutions. Funding for the guideline must be clearly stated,

along with full disclosure of the members of the Guidelines Panel and the Secretariat, and their declarations of interest.

If no other funder is identified, guidelines selected by GAB for further development may be offered financial support by EHIF. Regardless of the source of funding, guideline developers are encouraged to submit their proposals so as to benefit from the methodological support of the framework. In order to receive final approval from GAB for a guideline, the current process and methodology has to be clearly followed by the guideline developer regardless of the guideline financing body.

The guideline development process and methodology is presented in more detail in this handbook. For better understanding and clarity, process charts and templates are also presented herein.

The guideline development process

The steps and involvement of various members of the guideline development group are interrelated (see fig.1 *Diagram of the order in the guideline development process*) and not necessarily sequential (see fig.2 *Flow diagram of the guideline development process*). The guideline panel and supporting groups (e.g. methodologist, health economist, secretariat, administrative support) work collaboratively, informed through stakeholder involvement. They report to the GAB.

Fig.1 Diagram of the order in the guideline development process

While deciding how to involve stakeholders early for priority setting and topic selection, the guideline group must also consider how developing formal relationships with the stakeholders will enable effective dissemination and implementation to support uptake of the guideline. Furthermore, considerations for organization, planning and training (for Secretariat and Panel) encompass the entire guideline development project, and steps such as documenting the methodology used and decisions made, as well as considering conflict-of-interest occur throughout the entire process.

fig.1. Flow diagram of the guideline development process

I Guideline development groups

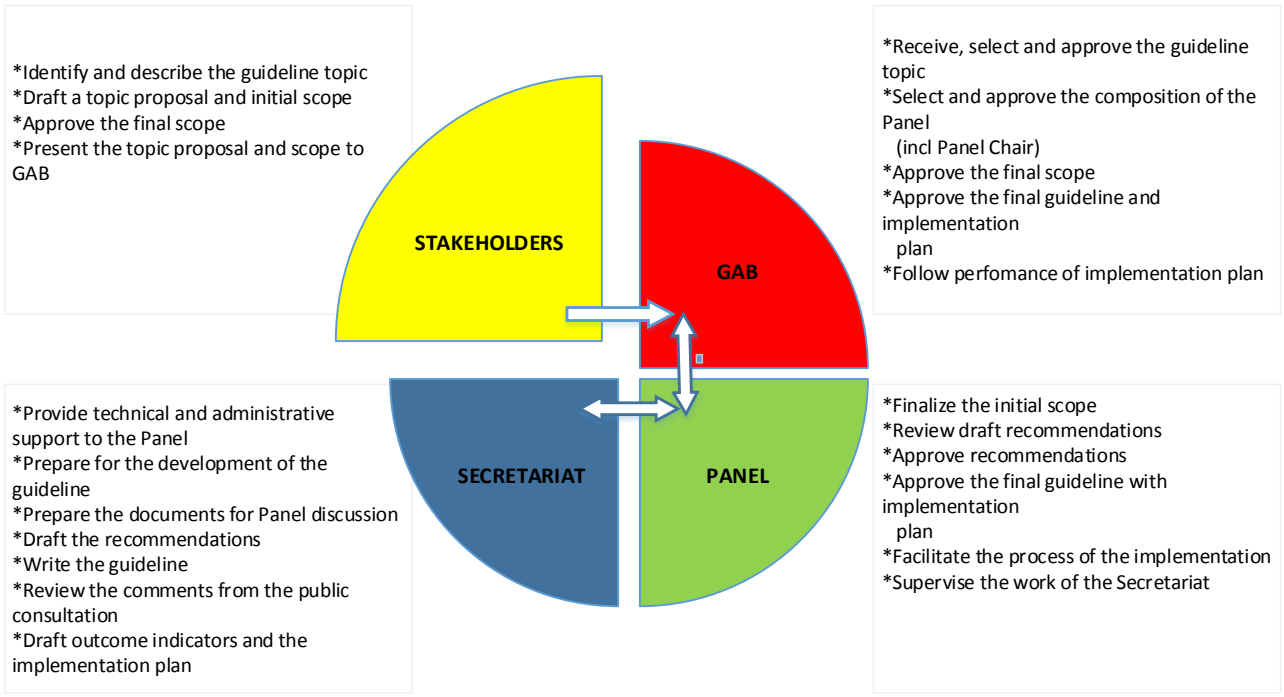

Fig.3: Diagram of the responsibilities of different stakeholders in guideline development process.

1. Guideline Advisory Board (GAB)

The GAB is created by the authority of the EHIF to act as one of its advisory committees. GAB consists of representatives of various educational and research institutions, medical societies, and an another organizations. The aim of GAB activities are to improve the availability and quality of patient care at different levels with cost-effective and evidence-based clinical guidelines that take into consideration the local costs and community values.

1.1 Tasks of the GAB

- ✓ Receive and choose guideline topic(s) presented with initial scope to be financed and/or to be supported by EHIF;
- ✓ Consult and approve the composition of the Guideline Panel and nominate the Chair of the Panel and Chair of the Secretariat;
- ✓ Approve the draft scope presented by the Panel;
- ✓ Evaluate declarations of interest (DOI, Appendix 1) and manage the conflicts of interest (COI) of the Chair, the Panel, and Secretariat members;
- ✓ Approve the final scope presented by the Panel;
- ✓ Approve the final guideline with its implementation plan;
- ✓ Regularly assess performance of the implementation plan.

The Dean of the Faculty of Medicine at the University of Tartu or his/her nominee leads the GAB. The GAB is created by the authority of the EHIF to act as one of its advisory committees. The work of the GAB is technically supported by the EHIF.

1.2 Composition of the GAB

GAB should include members nominated by the following institutions:

1. Faculty of Medicine, University of Tartu
2. Estonian Medical Association
3. Estonian Society of Family Physicians
4. Estonian Nurses Association
5. Estonian Hospital Association
6. Estonian Chamber of Disabled People
7. Institute of Public Health, University of Tartu

8. National Institute for Health Development (NIHD)
9. Estonian Health Insurance Fund (EHIF)
10. Ministry of Social Affairs (MoSA)
11. State Agency of Medicines (SAM)
12. Health Care Colleges

All members of the GAB are selected for the 3 years and required to complete declaration of interest forms before the process of topic selection is undertaken each year (Chapter I-4: *Management of declarations and conflicts of interest*).

Members of the GAB should meet as needed but at least four times per year. to consider and approve topics; to review progress, provide guidance, if necessary, and approve the final guideline for implementation.

2. The Guidelines Panel

The Guidelines Panel (hereafter "Panel") approve the recommendations in the guideline and endorse the final guideline document for approval by the GAB. Another important task of the Panel is to facilitate the implementation of the guideline at country level.

2.1 Tasks of the Panel

- ✓ The Panel is expected to read the material and provide feedback to the secretariat before the meetings. Lack of comments is considered as agreement to the material.
- ✓ Comment on the initial scope selected by the GAB and finalize it (including the formulation of clinical questions and choosing outcomes), taking into account the views of stakeholders. During the development of the questions for the guideline, the Panel has to consider which clinical questions may require information from existing guidelines or from systematic reviews.
- ✓ Approve recommendations, taking into account values and preferences, according to GRADE, and cost implications.
- ✓ Review draft recommendations based on the presented evidence with GRADE, with explicit consideration of the overall balance of risks and benefits. The assumption for the Panel is that the research evidence to support a particular recommendation is *global,* whereas costs, values and preferences, and feasibility of recommendations are *local* considerations, and therefore should be the basis of adaptation of international recommendations for local situations.
- ✓ Decide on consultation and peer review needed for the draft guideline.
- ✓ Agree on the primary methods for implementation and indicators for measuring the use of the guideline.

- ✓ Facilitate the process of implementation (i.e. to act as opinion leaders for and advocates of the guideline).
- ✓ Coordinate the work of the Secretariat by appointing a member of the Panel to work closely with the Secretariat.

Methodology training will be provided after approving the composition of the Guideline Panel and nominating the Chair of the Panel by the GAB. Agenda of the training will provide:

- Information about the guideline development process and shortly describe group processes.
- Workshops of different electronical tools for working groups (Doodle (time planner), skype (attending on meetings), OneDrive (document sharing), Zotero (management references)
- Defining the scope by formulating clinical questions (PICO)
    - Understanding the strategies for prioritizing topics in guidelines and appropriate ways to address them.
    - Understanding PICO, choose outcomes and consider possible resource implications.
- Overview of the methods for finding and evaluating evidences
    - existing guidelines (AGREE II tool)
    - systematic reviews and meta-analysis (ROBIS tool)
    - randomized controlled trials, other sources of evidence
- Moving from evidence to recommendations:
    - Understanding the key criteria when moving from evidence to recommendations including resource implications, equity, feasibility, values and preferences and the balance of benefits and downsides.
    - Workshop of using GRADEpro.com
- Making recommendations:
    - Guideline Simulation
    - Applying the key criteria when moving from evidence to recommendations

2.2 Composition of the Panel

The Panel should be multidisciplinary and should incorporate representatives of specialities involved in the relevant guideline. It should also include representatives of patient and/or consumer advocacy groups. Patients may be

familiar with the topic and its treatments based on personal experience and may be able to provide information and evidence relative to the guideline.

The initiator of the guideline presents the potential composition of the Panel and the name of the proposed chair to the GAB for approval. The GAB may deliberate on the composition of the Panel.

The Panel should include:

- ✓ medical experts;
- ✓ methodologists;
- ✓ health economist;
- ✓ representatives from key stakeholders and organizations involved in implementation, including:
  - representatives from consumer or patient associations;
  - representatives from the medical faculty of a university;
  - representatives of organizations involved in the health-care process and who are likely to be end-users of the guideline.

The size of the Panel depends on the topic of the guideline, but is generally up to 20 persons. The size of a Panel should be small enough for effective group interaction, but large enough to ensure adequate representation of relevant views.

2.3 Roles of Panel members

- ✓ **Medical experts** should represent the perspective(s) of health-care professionals, as well as social care and other professionals, where relevant, involved in the care of patients affected by the guideline topic; detailed evidence research expertise is not necessary, although an understanding of evidence-based medicine is essential.
- ✓ **Methodologists** are experts in assessing clinical evidence and developing guidelines, should be included as appropriate. Inclusion of a methodologist in a leading role, particularly one with experience in the guideline development process, is recommended to explain to the panel the evidence retrieval process and to guide the process of formulating recommendations.
- ✓ **Consumer or patient representatives** from patient's rights organizations (or a representative of the patient with the relevant chronic condition) – represents the view of the patient(s) with the relevant condition.
- ✓ **Medical faculty from a university** should be included for their related educational activities and implementation.

- ✓ **Managers and other health professionals** represent the view of the health-care services and provide expert opinion on the implementation of guidelines.
- ✓ **Health economists or bio-statisticians** provide an analysis of the costs of health services, cost-effectiveness, data on the provision of health care services and medicines, and so forth.

Panel members are asked to make a commitment to attend as many meetings for the guideline development process as possible, in order to ensure continuity and effective participation in the process. However, if necessary, Panel members may nominate an alternate to attend discussions, provided the alternate member is fully briefed on the material to be discussed. Alternate panels are also required to complete and submit a declaration of interests.

2.4 Chair of the Panel

The choice of the Chair of the Panel is important to ensure that the Panel will be able to work effectively. In most situations, groups work most effectively if the Chair has knowledge of the content, but who also has particular expertise in facilitating groups and interpreting evidence. People who are experts in the content area of the guideline and who have strong views about interventions or aspects that may be included should not chair a guidelines panel. The selection of a co-chair to cover these relevant aspects may be appropriate. A Panel may also be chaired jointly by a methodologist and a content expert, both of whom may agree jointly how to manage the meetings as co-chairs. Panel chair should use on the meetings the Panel chair's checklist (Appendix 2). Panel chair will participate in publishing an article (at least 3,000 characters) in the National Medical Journal and EHIF website after the GAB has approved the Clinical Guideline.

2.5 Panel meetings

To be effective, the Panel will need to convene at least 4-5 face-to-face meetings. The purpose of the first meetings are to develop the clinical questions so that the scope of the proposed guideline may be finalized. In followed meetings after approving of the scope by the GAB, the Panel needs review recommendations based on evidence prepared by the Secretariat. It takes generally 6-7 meetings (approximately approving recommendations to 3 clinical questions in each meeting). A final meeting might include approving the final guideline, indicators for assessment of implementation of the Clinical and Patient's guidelines (sometimes as well relevant Clinical Pathway), and finalizing plans for dissemination. Additional consultations (outside group meetings) may be held through electronic communication.

The scope of the meeting must be always clearly laid out at the start, including:

- what the ground rules will be (there should be no discussion about the process; i.e. members of the Panel agree to the process when they agree to become a member).
- what is expected from meeting participants;

- what needs to be achieved during the meeting;
- what can be done in the intercessional periods;
- what follow-up will take place with meeting participants.

A quorum for the meeting constitutes of three-fourths of the members being present. Decisions are taken based on consensus, however voting may be used to guide the development of the consensus. If voting is required, a majority (at least three-quarters) of Panel members must vote for agreement. When consensus cannot be reached through discussion, the Secretariat may have to do additional work, including further searches, and the topic will have to be discussed at the next meeting of the Panel. If the Panel has reached final agreement on a recommendation, then the recommendation will not be re-opened for discussion at a later date, unless there is new and significant evidence that needs to be considered. An example of this situation might be the publication of a new trial on an intervention that shows an effect in the opposite direction to previous studies.

<u>If the purpose of the meeting is to formulate recommendations following documents need to be prepared to the Panel:</u>

- *evidence profiles* (see Appendix 3a for an example based on the Guideline Development Tool)[2] prepared by the Secretariat two weeks (ideally) before the meeting;
- example based on the GRADEpro Guideline Development Tool) prepared by the Secretariat in consultation with the guideline panel before the meeting, ideally two weeks before the meeting;
- at the meeting, present draft recommendations that have been prepared by the Secretariat (meeting participants may comment on these and refine them).

A record of the meeting should be taken and should include the following information: who attended the meeting; what was the agenda; what actions were requested; what decisions were taken; and what the next steps will be, as well as any changes in panellists' declarations of interests. Evidence tables or summaries presented at the meeting may be appended to the meeting record. The minutes should be distributed to those who attended the meeting and may be made available online for easy access and reference.

3 Secretariat

3.1 Tasks of the Secretariat

- ✓ Prepare for the development and writing of the clinical- and patent's guideline, according to the Panel's guidance.

[2] GradePRO Guideline Develpoment Tool software is available and may be used without cost, http://gradepro.org/

- ✓ Provide technical support for developing the guideline, including preparation of documents that will aid the Panel in their decision-making; evidence retrieval for recommendations (GRADE); indicators, and implementation plan.
- ✓ Review the feedback obtained from any public consultation, summarise the comments and proposals, propose any responses, and summarise the information for the Panel to review.
- ✓ Provide administrative support for Panel meetings, keeping minutes, drafting meeting reports, etc.

Members of the Secretariat need skills in assessing and summarising clinical evidence, evaluating cost information and economic studies, and preparing concise reports. Training in these skills will be provided if necessary.

3.2 Composition of the Secretariat

Members of the Secretariat are identified in co-operation with the Medical Faculty at the University of Tartu and EHIF. The Secretariat should include five to six people, who are representatives of the specialities covered in the current guideline, as well as scientific-technical methodologists, health economists from EHIF, and an administrative assistant.

3.3 Roles of the Secretariat members

- ✓ **Representatives, including methodologists, of the specialities covered in the current guideline**: development of the preliminary recommendations based on clinical questions and evidence retrieval and writing the draft guideline based on the Panel's guidance.
- ✓ **EHIF's health economists**: assess the cost effectiveness and cost (budget) effects of the recommendations in the guideline.
- ✓ **Administrative support team**: works with the GAB, Secretariat, Panel, provides administrative support, arrangement of the meetings, arrange access to databases, organizing e-voting's if necessary, appropriate trainings, collecting DOIs etc.

3.4 Chair of the Secretariat

The initiator of the guideline presents the potential chair of the Secretariat to the GAB for approval. The choice of the Chair of the Secretariat is important to ensure that the secretariat will be able to work effectively. In most situations, groups work most effectively if the Chair has knowledge of the particular expertise in guideline development methodology, scientific research, and finding, evaluating the evidence.

Chair of the Secretariat should be able to:

- manage and coordinate the work of the members of the Secretariat (including selecting and proposing the inclusion of a member of the Secretariat or the process of deleting, taking minutes, distributing and presenting evidence profiles (Appendix 3a), EtD (Appendix 3b), draft recommendations to the Panel by the timetable set by GAB;
- participate in drafting the scope of the guideline;
- participate in clinical guidelines working group meetings;
- after approval the scope of the guideline by the GAB draw up an action plan for clinical- and applicable patent's guideline (and relevant Clinical Pathway's) development (setting out the specific activities of deadlines and responsibilities). The chair also monitors the execution of the action plan;
- draw up a basic literature search strategy (Appendix 4) and summarizes search and selection process (see below Fig 4);
- manages and coordinates the preparation of the Clinical guideline's draft and Patient's guideline;
- to organize the assessment of the evidence by the various tools (AGREE II, ROBIS, GRADE, Chapters II-3, II-4);
- identify the questions that need an economic assessment;
- publish an article (at least 3,000 characters) in the National Medical Journal and EHIF website after the GAB has approved the Clinical Guideline.

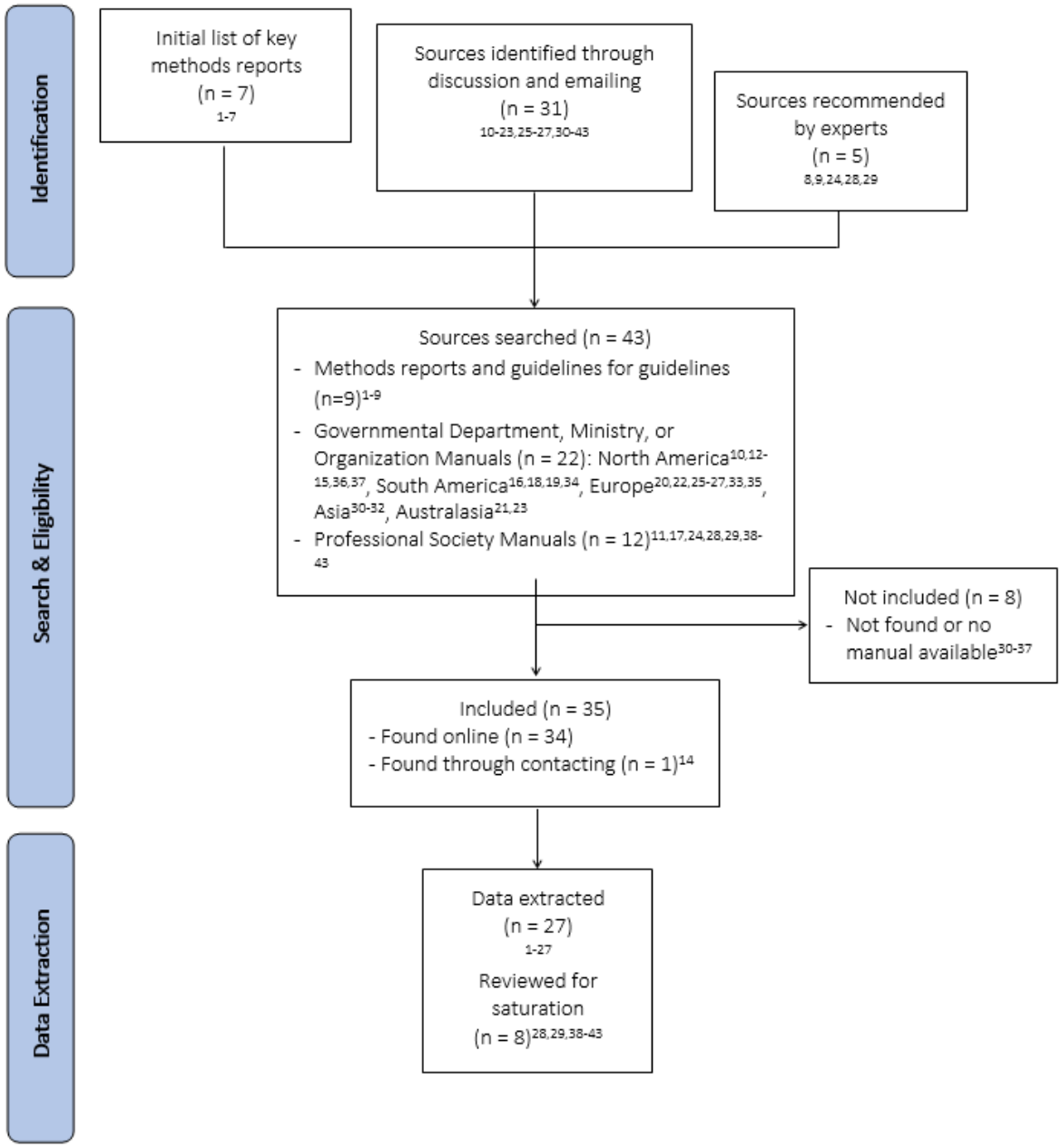

Fig 4: Search and selection process[3]

3.5 Secretariat meetings

Members of the Secretariat should participate in Panel meetings and present requested materials to the Panel.

Meetings of the Secretariat should be held electronically (e.g. Skype videoconferencing) in order to save resources and time. However, actual physical

[3] Holger J. Schünemann, MD, PhD et all (2014) Guidelines 2.0: Systematic development of a comprehensive checklist for a trustworthy guideline enterprise, CMAJ. Feb 18; 186(3): E123–E142. doi: 10.1503/cmaj.131237

meetings are suitable from time to time e.g. introductory meeting at the beginning of the Secretariat's work or where there is a need for more intensive group work, like formation of the evidence summaries, etc.

Meetings of the Secretariat should be held after each phase in the guideline's development process in order to discuss deliverables and outcomes, and to agree on further working processes for the next phase. These should include:

- ✓ discussion of the guideline scope in order to form a basic strategy for a literature search (Appendix 4);
- ✓ primary screening of retrieved guidelines in order to select papers for assessment using the AGREE II instrument[4] (Appendix 5a Table format for mapping guidelines to scope questions, Appendix 5b Summary tables of recommendations of guidelines and Chapter II-3.3);
- ✓ creation of a web-based search strategy for primary references (i.e. reports of clinical trials, systematic reviews, etc.) for questions for which there is no available material from guidelines. Search strategies and their results must be clearly documented (Fig 4, Appendix 4, 6, 7a);
- ✓ clarification of discrepancies between assessments[5] and mapping the availability of evidence for each question (Appendix 7b Robis instrument);
- ✓ appraisal of the primary references with the help of the GRADE approach (Chapter II-4, Appendix 3a, Template of Evidence profile);
- ✓ use GRADE to draft recommendations (Chapter II-4, Appendix 3b, EtD);
- ✓ creation of evidence summaries for each question and identification of questions requiring an economic appraisal;
- ✓ introducing the results of the economic analysis and incorporating this into the evidence summary;
- ✓ discuss preliminary feedback from the Panel Chair about evidence summaries and amending them accordingly;
- ✓ formation of a final evidence summary for the panel members to prepare questions specific to the guideline[6] (Appendix 3b, EtD);
- ✓ suggesting a process and/or outcome indicators for monitoring of the implementation of the guideline;
- ✓ preparation of an implementation plan (Appendix 8).

Members of the Secretariat are also required to complete and submit a declaration of interests.

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[4] Appraisal of Guidelines Research and Evaluation Instrument. See http://www.agreecollaboration.org/instrument/.

[5] Each guideline should be assessed by at least two assessors. See Section II-3.3 Retrieving and assessing existing guidelines

[6] The summary should be sent to the Panel Chair at least two weeks prior to the relevant meeting.

4. Management of declarations and conflicts of interest

According to the World Health Organization, a declaration of interest is the disclosure of any potential or actual conflicts of interest that include financial, professional, or other interests relevant to the subject of the work or meeting in which an expert may be involved and any interest that could significantly affect the outcome of the meeting or work. The declaration of interest must also include any relevant interests of others who may, or may be perceived to, unduly influence the expert's judgment, such as immediate family members, employers, close professional associates, or any others with whom the expert has a substantial common personal, financial, or professional interest.

A declaration of interest indicates a Panel, Board, and Secretariat members' financial or personal interests in an external company or organization. While there are no rules prohibiting financial or personal ties to companies or organizations, these ties may represent a conflict of interest if the company or organization has an interest in a product that is the subject of the guideline under development. Therefore, it is important that:

- ✓ Each nominated Panel and Secretariat member should complete and submit a declaration of interests (DOI) (Appendix 1: Declaration of Interests[7]), to the GAB. The GAB will then decide whether the declaration contains any conflicts that should result in the exclusion of a proposed Panel or Secretariat member.
- ✓ Once the Guideline Panel, chair of the Secretariat is approved by the GAB, the administrative assistant should collect all DOIs before the first meeting. If there are any changes, the administrative assistant, in coordination with the Chair, should leave enough time for the Chair to intervene, if necessary. If a nominee has a conflict of interest, several possibilities exist. First, the nominee may be invited to participate, but only if their conflict is publicly disclosed. Second, the nominee may be asked not to participate in a particular portion of the meeting, discussion, or work that is directly related to their conflict. Or, third, the nominee may be asked to withdraw their nomination entirely.
- ✓ At the first panel meeting, and at all subsequent meetings, each Panel member and chair of the Secretariat should verbally report potential conflicts of interest. All Panel members and any individuals who have direct input into the guideline should update their DOI form before each panel meeting. Any changes to the DOI should be recorded in the minutes of the meeting.
- ✓ Any conflicts of interest that are identified should be managed according to the rules agreed to by the GAB. If a panelist has a conflict of interest, the panelist has the same options as those outlined for nominees.
- ✓ DOI summary must be submitted for each full guideline as an integral part.

[7] http://ravijuhend.ee/uploads/userfiles/Huvide_deklareerimise_vorm_taidetav(2).pdf

II Development of the Clinical guidelines

1. Topic proposal and selection

A ‘topic’ of a guideline specifies the disease or condition that will be covered by the guideline, as well as the target population and setting in which care will be delivered; e.g. *'the management of type 2 diabetes in patients over 40 years of age in primary care*'.

1.1 Making a topic proposal

- ✓ Topics for guideline development may be proposed by the provider of health care services and interested parties, including medical societies, EHIF, the Medical Faculty of the University of Tartu, the National Institute of Health Development, MoSA, etc. (named here as well *Stakeholders*) Is larger agreement that for pharmaceutical manufacturers is not appropriate to initiate topics, as this may present major conflicts of interest. The individual or organization proposing the topic is subsequently called “the initiator”.
- ✓ Topic (together with their initial scope), can be presented by the initiator to the GAB[8] throughout the year. Proposals for the current year must be provided no later than 1st of February (Appendix 9).
- ✓ Topic may be triggered by many different inputs: regular audits; feedback from practitioners; variations in care; guidelines being issued by other entities that need to be adapted; introduction of new interventions; emerging health problems; etc.
- ✓ Topic proposal must include statistical data. Acquiring this data will require active communication between the initiator and potential stakeholders, including EHIF.
- ✓ Topic proposal must have digital signature from representatives of involved professional societies.

1.2 Selecting topics for development

Topics, which EHIF may finance, are selected by GAB for development into guidelines. In selecting topics, GAB takes into account the initial scope of the topic(s), consideration of needs of different stakeholders, availability of existing systematic reviews and guidelines that could be used to adapt or develop guidelines. In the process of choosing topic(s), financing and applicability of further guidelines should be taken into account, particularly with regard to potential resource and organisational implications. Understanding and evaluating any implications helps to avoid a situation where GAB chooses to finance a guideline topic which is either not feasible to implement or is not affordable to the health system.

[8] More information: http://ravijuhend.ee/koostajale/teemaalgatus/

Based upon the criteria listed below, the GAB will assess the topic proposals using the draft scope documents (topic proposal with initial scope) presented to them by 1st of February. The GAB members will score all proposed topics based on importance and usefulness (e.g. if there are three different topics to choose between, then the most valuable topic receives three points and the others, two and one points, respectively).

The GAB will evaluate topics based on their assessment of:

✓ Problem statement and the purpose of the guideline (Appendix 9)

- The problem statement is drafted by the initiator based on the information listed below. For example, "*persons having condition X in Tartu area are hospitalized more frequently and their average prescription cost is different from other regions in Estonia*." Therefore, the purpose of the guideline may be, "*to guarantee up-to-date treatment with equitable costs for persons with condition X irrespective of region*."
  - Burden of disease
    - the population suffering the disease/condition in Estonia (incidence, prevalence, mortality, etc.)
    - the resource impact of the disease/condition in Estonia
  - Variations (practice variation and variations in health outcome by different):
    - regions in Estonia
    - providers in Estonia
    - level of care (primary care vs. specialist services)
    - patient populations, including subgroups
  - International practice compared with Estonia
    - variation in treatment costs (regions, providers, level of care, patient populations, etc.)[9]
    - service treatment (all treatment costs within a certain period)
    - pharmaceuticals
    - hospitalization (rate, length of stay, etc.)
  - Potential
    - potential for modernization of current practice
      - availability of new interventions (including diagnostic tests and strategies)

[9] Treatment cost analyses can be conducted using data from the EHIF database, which may be obtained on request.

- availability of new evidence that will likely change the practice
- availability of new service delivery

– potential result of successfully implemented guideline

- measurable impact on health indicators
- more cost-effective use of resources

✓ Initial scope prepared by initiator (see Appendix 10a: Template for scope)

✓ Relationship of topics and scope to health related government priorities

The GAB members will score[10] (on a 7-point scale: 1 not important to 7 most important) all proposed topics based on importance and usefulness (e.g. if there are three different topics to choose between, then the most valuable topic receives three points and the others, two and one points, respectively). Scores of the proposed topics are calculated by summing up all the scores of the individual and by scaling the total as a percentage of the maximum possible score for that topic.

[10] By AGREE II http://ravijuhend.ee/uploads/userfiles/file/AGREE/AGREE%20II_eng.pdf, IV. Scoring the AGREE II, p 9

For example:

If 4 appraisers give the following scores for Domain 1 (Scope & Purpose):

	Item 1	Item 2	Item 3	**Total**
Appraiser 1	5	6	6	**17**
Appraiser 2	6	6	7	**19**
Appraiser 3	2	4	3	**9**
Appraiser 4	3	3	2	**8**
Total	**16**	**19**	**18**	**53**

Maximum possible score = 7 (strongly agree) x 3 (items) x 4 (appraisers) = 84
Minimum possible score = 1 (strongly disagree) x 3 (items) x 4 (appraisers) = 12

The scaled domain score will be:

$$\frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}}$$

$$\frac{53 - 12}{84 - 12} \times 100 = \frac{41}{72} \times 100 = 0.5694 \times 100 = 57\ \%$$

If items are not included, appropriate modifications to the calculations of maximum and minimum possible scores are required.

The GAB is under no obligation to make a selection among topics proposed, particularly if the topics are not potential subjects for a guideline (i.e. there is no need for a local guideline in a particular topic, there is no potential for changes, etc). The GAB will document the arguments for selecting or not selecting particular topics for guideline development and will send their response to the initiator. A topic that is rejected may be resubmitted for consideration in the following year as a revised proposal.

After selecting topic for the new guideline, the GAB will consult and approve the composition of the Panel and Chair of the Secretariat.

2. The scope of the guideline

The scope provides a framework within which to conduct the guideline development work. The Panel may revise the initial scope based on the importance of the questions and their outcomes, the potential evidence available, or the potential for recommendations that will be useful in the Estonian health-care context. It is critical not to expand the scope too much as it determines the feasibility of completing the guideline in a timely manner.

Creating a scope for a guideline is done in stages:

1. Drafting the initial scope
2. Consulting with stakeholders about the draft scope
3. Finalizing the scope

2.1 Preparing the scope

The initial scope, with draft PICO questions and perceived outcomes (see below), is prepared by the initiator of the clinical guideline. The scope and outcomes are finalized by the Guideline Panel, in cooperation with the GAB, and signed off by the GAB.

After the topic is defined by the initiator, the aspects of care that the guideline will cover should also be defined, including:

- ✓ population to be included or excluded (e.g., specific age groups or people with certain types of disease);
- ✓ the different types of interventions (e.g. diagnostic tests, surgery, rehabilitation, lifestyle advice) to be included or excluded.
- ✓ the outcomes that will be considered (benefits and potential harms to patients, impact on health insurance, societal perspective);
- ✓ health-care settings (primary or specialized care);
- ✓ information and support for patients and their care-givers and health care providers;
- ✓ links with other relevant guidance. Are there any similar guidelines available in Estonia in this particular therapeutic area? If so, will the new guideline replace or supplement the existing one(s)?

On the basis of these aspects, formulate an initial scope that:

- ✓ provides an overview of what the clinical guideline will include (e.g. pain treatment in lung cancer) and what will not be covered (e.g. chemotherapy in lung cancer);
- ✓ identifies the key questions (clinical, as well as organizational, regulatory, etc). It is appropriate to formulate the questions using the PICO format (Chapter II-2.2: *Formulating questions for the sco*pe);
- ✓ chooses and rates the outcomes (Chapter II-2.3: *Choosing and rating outcome*s, Appendix 10b *Rating table for outcomes*);
- ✓ sets the boundaries of the development process and provides a clear framework to enable the work to stay within the agreed outcomes;

- ✓ ensures that the guideline will be of reasonable size (no more than 20 key questions suggested) and can be developed within a specified time period;
- ✓ ensures that all potential stakeholders are consulted;
- ✓ helps find out if there are any existing guidelines in Estonia covering this topic, if up-to-date evidence is likely to be available on the topic, and
- ✓ helps to decide the title of the guideline.

A template for the scope can be found in Appendix 10a.

2.2 Formulating questions for the scope

The selection of questions (and their components) that are to be addressed in the guideline has major consequences for the scope of the guideline. The questions will drive the direction (inclusion and exclusion of data) and determine the type of information that will be searched for and assessed. The PICO questions are the starting point for formulating the recommendations. It is very important that the questions are clear and well defined, and that there is agreement about them among Panel members. The Scope section in GRADEpro[11] can be used to define the scope and brainstorm questions.

It is helpful to start thinking about questions into three main categories (with examples):

Definition/background questions

- What is human papilloma virus (HPV) infection?
- What are the anatomical causes of low back pain?

Facts/foreground questions

- What is the impact of HPV vaccine on cervical cancer, adverse effects, etc.?
- What is the impact of home versus hospital treatment of patients with deep venous thrombosis on death, pulmonary embolisms, recurrence, burden and pain?
- What is the impact of a national hypertension screening and treatment program on death, stroke, myocardial infarction…?

Decision questions

- Should we use HPV vaccine?
- Should Estonians be screened for hypertension?

[11] http://gradepro.org/

Foreground questions typically focus on health effects. Recommendations and decisions are based on the answers to these foreground questions but require additional information in a guideline (e.g. information feasibility, cost-effectiveness). Other information that is needed to support decisions relate to values and preferences of people, resource utilization, equity, feasibility and acceptability. In addition, some information gathered about the background questions can inform how the guideline will be adapted to the issue or topic, values and preferences, clinical needs, and baseline risks. Therefore, guideline panels should focus on clear foreground questions that, together with other information, lead to unambiguous recommendations to support health care decisions.

The questions to be covered by the guideline should be identified on the basis of clinical or policy needs and input from clinicians and other experts. Input from consumer or patient groups may also be helpful. Generally, questions should focus on areas of controversy that need to be answered by the guideline or on areas where changes in policy or practice are needed.

The initial list of types of question to be covered will probably be a long one. Some examples could be:

- ✓ What are the phenomena associated with the problem? (background)
- ✓ What causes the problem? (background)
- ✓ What is the frequency of the problem? (degree of problem or prevalence)
- ✓ Who has the problem? (diagnosis)
- ✓ How it can be prevented? (prevention)
- ✓ What happens if someone gets the problem? (prognosis)
- ✓ How can we treat the problem? (intervention)
- ✓ What policies should we introduce to alleviate the problem? (policy intervention)

Questions contribute to achieving the purpose of guideline.

To turn these general questions into questions that can be answered, the PICO framework is useful:

Table 1: PICO framework

Factor	Descriptor/Question	Example
Population	What factors are essential (see next table)?	In adults (>18 years of age) and the elderly (over 75 years of age) with confirmed hypertension…
Intervention	Specific intervention?	…does dietary advice concerning salt restriction…

Comparator	Compared with doing nothing or with standard treatment	…compared with no salt restriction…
Outcome	Patient-relevant outcomes, including both benefits and potential side effects and over what period of time (e.g. mortality at two years)	…lower blood pressure and/or reduce mortality?

Table 2: Explanations to identify elements or items in the PICO framework (Schünemann et all [12]).

Domain	Subdomain	Item(s)
Population	Disease and co-morbidities	Primary condition of interest Secondary conditions of interest (co-morbidities)
	Non-modifiable person or population characteristics	Age Gender Genetics Ethnicity
	Modifiable person or population characteristics	Anthropometric (weight) Type of community or organization
	Environmental and geographic characteristics	Urban on non-urban Exposure to toxins (may be a population defining factor that can be removed through an intervention)
	Setting	Health care system and provision (tertiary care, secondary, primary care) Regulatory environment
Intervention (may separate planned from naturally occurring intervention	Type of intervention	Drugs/medication Behaviour Policy change (Removal of toxins)

[12] Schünemann HJ, Tugwell P, Reeves BC, Akl E, Santesso N, Spencer F, Shea B, Wells G, Helfand M. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. Research Synthesis Methods 2013; 4:49-62, 2013.

or exposure)		Non intended effects of law-making Components of the intervention (What are the components, who is administering or implementing the intervention, what is the intensity
	Components of the intervention	What are the components Who is administering or implementing the intervention What is the intensity and duration
	Naturally occurring intervention	Type of exposure
Comparator	No active comparison	Drugs: Placebo Usual care Current policy continues to be used
	Active comparison	Same as intervention
Outcomes	Health outcomes (beneficial and non-beneficial including burden)	How is the outcome measured (valid?) When is the outcome measured Surrogate or patient/population important
	Economic outcomes (resource use)	Resource units consumed
	System outcomes	

This format can also be used, with slight modifications, for questions on prevalence and incidence, aetiology (exposure-outcome) and diagnosis. For instance:

- In women in Estonia (**P**), what is the frequency of breast cancer (**O**)?
- In men over 40 years of age (**P**), what is the rate of lung cancer (**O**) in smokers versus non-smokers (**C**)?
- In babies born to HIV-positive women (**P**), does screening with a new rapid diagnostic test (**I**) compared to the reference test (**C**) accurately detect disease?

2.3 Choosing and rating outcomes

Once the clinical questions for the guideline have been defined, identify the key results that need to be considered in making the recommendations. Specifically define the outcomes for foreground questions and for the questions that will be *critical* for making decisions and recommendations. These results will also be used to guide evidence retrieval and synthesis. It is important to focus on the outcomes that are significant to patients, and to avoid the temptation to focus on those that are easy to measure and are often reported (unless these are also important). See here for training on outcome selection: http://fhsed.mcmaster.ca/onlineModules/GRADE/outcomes/

Step 1. Create an initial, comprehensive list of possibly relevant outcomes for each question, including both desirable and undesirable effects from the interventions that will be considered in the recommendations.

Step 2. With the group, score the relative importance of each outcome from 1–9. Rating an outcome 7–9 indicates that it is critical for a decision either to recommend or not recommend a particular intervention or diagnostic test. A score of 4–6 indicates that the outcome is important, while 1–3 indicates that it is not important. The average score for each result can be used to determine the relative significance of each outcome, although it is helpful to provide the range of results as well. Sometimes people with different perspectives (patients, physicians, researchers, policy-makers, et al.) have different opinions about which outcomes are important. Therefore, all these stakeholders should have an opportunity to contribute to the discussion on the selection of critical outcomes either by participation in the Panel or by consultation.

The following approach can be used for step 2 with the panel members.

- Rate the relative importance for each outcome on the 9 point scale below ranging from 1 (not important) to 9 (critical). You can use the same rating several times (i.e. same number for more than one outcome). Discuss outcomes ranked with wide range of importance. The same rating can be used more than once.
- Note: while most outcomes have some importance it can be difficult to consider all outcomes when making the final recommendation, therefore evidence will be gathered for important and critical outcomes and will be considered when making the final recommendation

Table 3: Rating the relative importance for each outcome (scala)

rating scale:								
1	2	3	4	5	6	7	8	9
⬆ of **least** importance								⬆ of **most** importance
of limited importance for making a decision (not included in evidence profile)			important, but not critical for making a decision (included in evidence profile)			Critical for making a decision (included in evidence profile)		

Step 3. Tabulate ratings by calculating the average score for each outcome. Provide these ratings to the panel so a decision can be made regarding which outcomes will be used for making recommendations. These ratings can be conveniently completed using electronic tools, such as a Microsoft Excel spreadsheet distributed by email, GRADEpro[13], or other open source solution (e.g. online survey applications (eFormular), which allow the user to prepare an interactive survey and send a link to participants).

2.4 Identifying resource implications

Once the key questions are formulated, the Panel should evaluate the resource implications for the potential interventions that may be recommended. This might include, for example, possible changes in costs due to new medicines or diagnostic tests, or possible outcomes, such as admission time to hospital. This step will provide information about cost effectiveness and budget-impact assessment that will be carried out by the Secretariat and included in the EtD (Appendix 3b). Further aspects of the evaluation of cost and resource use for recommendation development are in Chapter II-5.

2.5 Finalising the scope

Topic, together with the filnal scope, must be presented by the Panel to GAB according to the templates for scope (Appendix 10a) and implementation (Appendix 10b).

The GAB will assess the topic together with the initial scope documents and will or will not approve finalized scope for guideline development.

[13] http://gradepro.org/

3. *Evidence retrieval*

3.1 Evidence for guideline development

To promote quality of care, guideline recommendations need to be based on research evidence, consideration of costs, and the values and preferences of health-care workers and consumers. A summary of all relevant research evidence is essential when developing a recommendation and, ideally, the summary of research evidence should be based on a systematic review (see the flowchart Figure 5: *Evidence retrieval, assessment, and synthesis process*. *The process of evidence retrieval*). In contrast to narrative reviews, systematic reviews address a specific question and apply a rigorous scientific approach to the selection, appraisal, and synthesis of relevant studies. Systematic reviews, if conducted properly, reduce the risk of selective citation (the 'my favourite study' approach) and improve the reliability and accuracy of decisions.

Many guidelines-producing organizations rely on groups such as the Cochrane Collaboration for systematic reviews that can be used in guideline development. Some well-resourced organizations that develop guidelines, such as WHO and NICE, also commission reviews. In countries or organizations with limited resources, however, it is more practical and efficient to use reviews and recommendations from existing guidelines as the basis for local guideline development and only occasionally develop recommendations *de novo.* This is based on the assumption that research evidence to support a particular recommendation is usually *global*, whereas costs, values and preferences, and the feasibility of recommendations are *local* considerations, and therefore should be the basis of *adaptation* of international recommendations.

The clinical guidelines in Estonia will therefore be developed, including:

1. recommendations developed from published clinical guidelines that were created by independent national authorities (e.g., NICE) and that meet specified criteria.
2. recommendations developed from published clinical guidelines that were created by commercially funded specialty societies, and that follow standardized criteria for guidelines (provide evidence summaries and adequate descriptions of the processes used to manage conflicts of interest);
3. recommendations developed from existing systematic reviews.

All guidelines that are used as sources should be assessed for their quality using the AGREE II tool[14].

Systematic reviews that are used will be assessed for quality using the latest version of the ROBIS checklist[15], aimed at four broad categories of reviews

[14] http://ravijuhend.ee/uploads/userfiles/file/AGREE/AGREE%20II_eng.pdf
[15] http://www.robis-tool.info/

mainly within health care settings: interventions, diagnosis, prognosis, and aetiology.

It is anticipated that from time to time, guideline recommendations may be required when there is truly no evidence to support a decision. In these situations, the panel will need to document the reasons for developing the recommendation and the basis for their judgement. Such a recommendation may also be the basis for a proposal for research.

3.2 Prioritizing evidence retrieval

Whatever the source of the evidence, retrieving evidence to support every recommendation in a guideline may simply not be feasible. Therefore, it is important to identify priority questions or issues that the guideline should address (Chapter II-2: *The scope of the guideline*).

To avoid performing a duplicate search or creating a duplicate guideline, the process outlined below starts by 1) using existing guideline recommendations, and checking the evidence for them, then 2) describes the full process of developing recommendations based on systematic reviews, and 3) includes a process for undertaking systematic reviews. This third step should be carried out only when there is no existing basis for a recommendation and when the question is a major issue for the guideline to cover. The methodology of development of systematic reviews is not covered in this handbook. Preparation of systematic reviews should follow the Cochrane Handbook for Systematic Reviews of Interventions.[16]

The process of evidence retrieval, assessment, and synthesis is described and summarized in the figure further detail below (see Figure 5: *Evidence retrieval, assessment, and synthesis process*).

[16] The Cochrane Handbook for Systematic Reviews of Interventions is available at: http://www.cochrane.org/training/cochrane-handbook.

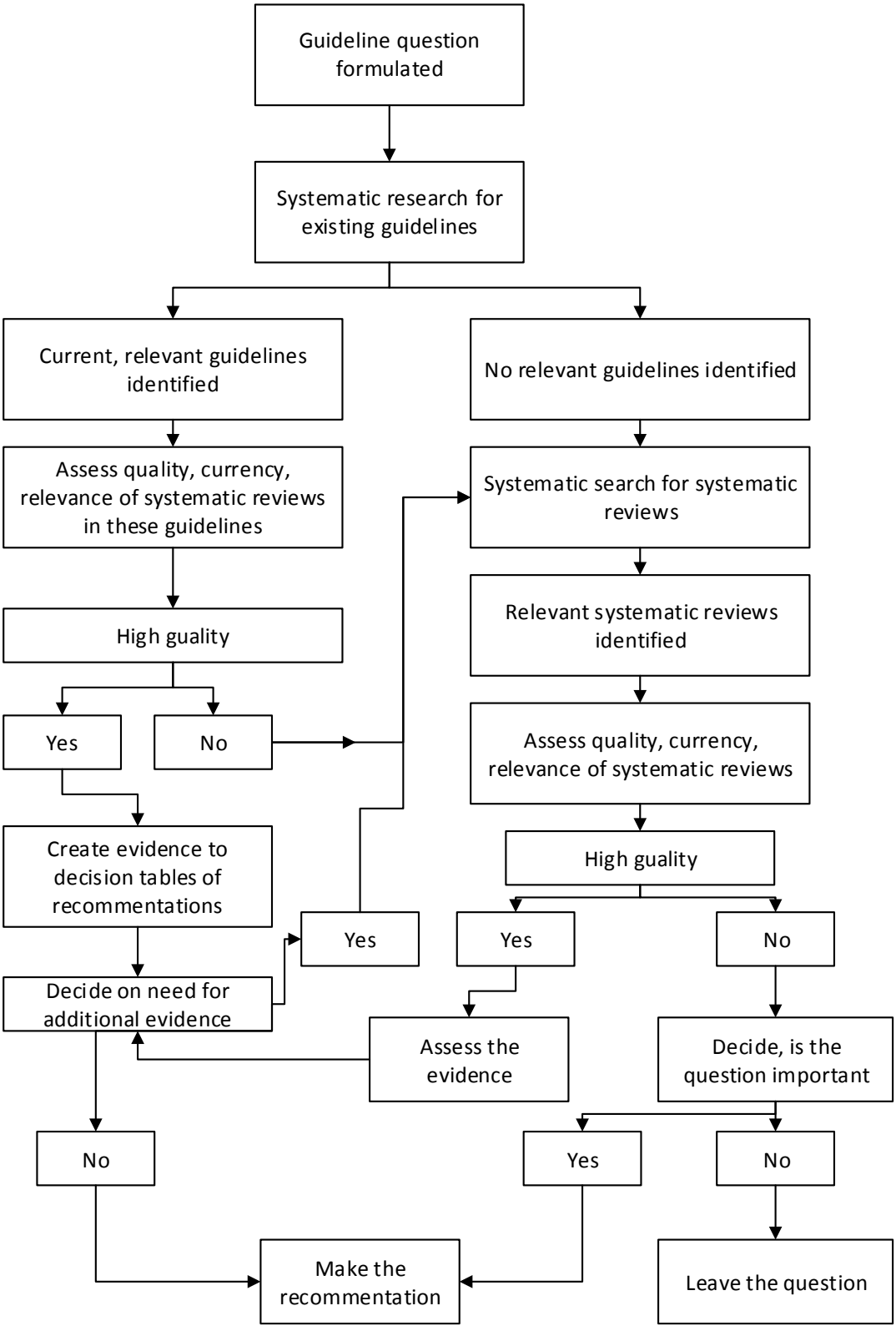


Figure 5: Evidence retrieval, assessment, and synthesis process

3.3 Retrieving and assessing existing guidelines

It is strongly recommended that the search for evidence should be carried out in consultation with an expert (i.e. a librarian, medical research assistant, et al.) in information retrieval to ensure the use of a sound search strategy.

Start by conducting a systematic search for existing guidelines. The initial search should be broad and without limitation, as guidelines can be difficult to find through electronic databases.

The following sources, in addition to Medline, should be searched:

- the National Guideline Clearinghouse - http://www.guideline.gov/
- the database of the Guidelines International Network (GIN)[17]-http://www.g-i-n.net/library
- GRADE Working Group Database: http://dbep.gradepro.org/
- websites of guideline-producing agencies:
    - Guideline International Network
    - National Institute for Health and Clinical Excellence (NICE): http://www.nice.org.uk
    - Canadian Agency for Drugs and Technologies in Health (CADTH): http://www.cadth.ca
    - Agency for Healthcare Research and Quality (AHRQ): http://www.ahrq.gov
    - Database of WHO guidelines http://www.who.int/publications/guidelines/en/
- Websites of specialist medical societies relevant to the topic and scope of the proposed guidelines

A sample search strategy for the initial search is provided in Appendix 4 and Appendix 6. It should include **Medical Subject Headings** (MeSH) terms for the content area (defined by disease, population, setting, and interventions specified in the scope document questions), as well as MeSH terms for clinical practice guidelines and reviews. See http://www.ncbi.nlm.nih.gov/mesh.

If there are several potentially relevant guidelines identified through the initial search, the Panel should be asked to advise the Secretariat on retrieval parameters. These can be limited by date of publication (e.g. only those guidelines published in the last five years), language, or refinement of the search terms. Prioritize sources that have GRADE evidence to decision frameworks.

[17] Access to this database is only available to members of GIN.

The search strategy used should be documented and should specify:

- the details of the databases (including web sites) searched, and the search strategy planned for each database;
- the details of each strategy as actually performed, specifying the date on which the search was conducted and/or updated (this description must be included in the final guideline).

The citation list resulting from the search strategy should then be screened to exclude obviously irrelevant publications. Potentially relevant citations should be retrieved as abstracts, if possible, and then further screening should be undertaken to identify possible guideline documents. These should then be retrieved in full text.

Relevant guidelines should then be assessed for the following aspects:

1) Are the guidelines based on explicit use of evidence?

- If not, they should not be used.
- If they are evidence based, are evidence summaries provided? (E.g., GRADE summary of findings tables and evidence profiles, or references to systematic reviews.)

2) Who funded the guideline development?

- If the funding was from commercial sources, what processes were used to manage conflicts of interest? If these are not described, the guidelines should not be used further, but there may be relevant systematic reviews or evidence profiles incorporated into them that may be helpful.

A summary of the publications assessed, and reasons for the exclusion of any, should be prepared by the Secretariat for review by the Panel at the first meeting to ensure that exclusion of publications is appropriate.

Publications or guidelines that are included following this initial screening need to be assessed in further detail for two aspects:

1) do the recommendations in the publications correspond to the questions in the proposed scope? An example of a table format for 'mapping' guidelines to scope questions is in Appendix 5a.

2) what is the credibility of the guideline, based on the AGREE II rating instrument[18]?

[18] http://ravijuhend.ee/uploads/userfiles/file/AGREE/AGREE%20II_eng.pdf

Ideally two members of the Secretariat should assess each guideline and the individual ratings should be compared. When possible, additional assessors are welcomed.

This assessment process should lead to the identification of a list of guidelines that may be used for developing local recommendations or as a source of evidence. The recommendations in these guidelines should be mapped in detail to the questions in the scope. The evidence used in each guideline as the basis for each recommendation should also be summarised.

If the recommendations and the sources of evidence are the same, the main considerations in deciding to adopt the recommendations locally will be based on factors of cost, values and preferences, and feasibility (Section II-6: Developing recommendations).

If there are very few guidelines (1-2) that make recommendations for a particular question, it will probably be necessary to review the references (systematic reviews and clinical trials) for these recommendations. In addition, if the guidelines are more than 2-3 years old, it is also possible that newer evidence may be available that might need to be considered. Pragmatic decisions will have to be made about how to supplement the evidence in existing guidelines with new evidence, if necessary. Advice on this should be obtained from the content experts on the Guidelines Panel. If it is necessary to search for additional evidence, then it may be practical to limit the search to a time period not covered already by searches made for existing guidelines.

If the recommendations in the guidelines that are used vary from each other, it is likely that further evidence retrieval will be needed. If the guideline has used GRADE profiles or Summary of Findings Tables as the basis for evidence presentation, it may be possible to update the evidence profile and then reassess the recommendation, adding in considerations of costs, local values and preferences, and feasibility.

If there are no usable existing guidelines or recommendations for a particular question, it will be necessary to retrieve existing systematic reviews.

3.4 Retrieving existing systematic reviews

3.4.1 Importance of systematic reviews

High quality systematic reviews reduce the risk of selective citation and improve the reliability and accuracy of decisions. If systematic reviews are to be used in guideline development, they should be assessed for quality.

The key features of a high quality systematic review are that it should describe:

- the search strategy used to identify all relevant published – and unpublished – studies;
- the eligibility criteria for the selection of studies;

- how studies will be critically appraised for quality;
- an explicit method of synthesis of results and, if feasible, a quantitative synthesis of the results of studies to estimate the overall effect of an intervention (meta-analysis).

3.4.2 Finding systematic reviews

The first step is to identify relevant systematic reviews for each of the questions (Appendix 4), using PubMed or a similar database. The PubMed "Clinical Queries" or "Special Queries" options permit specific searches to be set up to identify systematic reviews of different types of studies identified with MeSH terms (see http://www.ncbi.nlm.nih.gov/mesh). This includes searches of the Cochrane Database of Systematic Reviews.

As with searches for guidelines, the search strategy for systematic reviews needs to be broad initially, and not limited by language or year. The Panel should be asked for advice on any limits by date of publication. The search strategy used should be documented. The initial list of citations retrieved should be screened for relevance, and obviously irrelevant citations should be excluded. The remainder should be retrieved in abstract for further assessment, to identify a final list of reviews for potential use in developing recommendations that should be retrieved in full.

3.4.3 Assessing the credibility of systematic reviews

Once the reviews are retrieved, they should be checked for:

- potential commercial sources of funding. Any reviews funded explicitly by pharmaceutical companies should be excluded from use unless there is no alternative review on the same topic;[19]
- relevance to the questions to be addressed in the recommendations. If the review is clearly not relevant, it should be excluded;
- timeliness, as assessed by the date of the last update. If the review is of high quality but more than two years old, consider updating the review to include more recent evidence, depending on advice from the Panel about the likely existence of new evidence that will need to be included in the development of any recommendation;
- quality, which schould be assessed by using the ROBIS instrument[20], a standard critical appraisal instrument (Appendix 7b). Ideally, this should be done by two members of the Secretariat. Based on the ROBIS instrument, reviews may be excluded from further use if both raters agree that there

[19] Even then, they should be used with great care as the risk of selection bias for including studies or outcomes is very high!

[20] Whiting, P. *et all* ROBIS: A new tool to assess risk of bias in systematic reviews was developed. January 2016, Vol 69, Pages 225–234

were no prespecified criteria for including studies and there are concerns about the conflict of interest declaration. Otherwise, the reviews should be included. If there are several relevant systematic reviews, use the most recent one that is of high quality. If the review is of high quality but more than two years old, consider updating the review to include more recent evidence, depending on advice from the Panel about the likely existence of new evidence that will need to be included in the development of any recommendation.

3.5 Presentation of results and recommendations to the Panel

The Secretariat needs to prepare summary tables that include:

1) the recommendations from included guidelines (Appendix 5b Summary tables of recommendations of guidelines)

2) results relevant to each question and outcome from guidelines and systematic reviews (Appendix 3a Template of Evidence profile) to present to the Panel.

For summary tables of results from systematic reviews for each question and its outcomes (Appendix 6 *Presenting the results of a systematic review*), GRADE evidence profiles may be used, or study-by-study tables, using the template in Appendix 3b *(EtD)*.

The summary tables will need to be supplemented with short narratives that describe the nature of the evidence. An example of a narrative is: "*There are five guidelines that provide recommendations on question 5. The evidence used for the recommendations is derived from six systematic reviews; the most recent one was published in 2007. It included 16 randomised controlled trials (21 567 subjects) that compare treatment A with treatment B*."

For information, Appendix 6 (*Presenting the results of a systematic review*) summarises the general presentation of results in systematic reviews.

4. Grading the quality of evidence

Assessing the evidence retrieved is a crucial step that enables the guideline panel to formulate recommendations. The GRADE system is used for preparing evidence profiles and summary of findings tables (www.gradepro.org) which includes assessing the quality of evidence. GRADE also uses the terms "certainty in the evidence" or "confidence in the effect estimates" as alternative expressions for "quality of evidence".

GRADE is also used for developing recommendations by utilizing GRADE EtD (Appendix 3b *Evidence to decision framework*). The GRADE approach allows for a structured and transparent assessment of the quality of evidence for each outcome. For each question, there should be relevant data (from the systematic review) for all the outcomes (benefits and harms) that were rated as important supplemented by evidence about other criteria in the EtD. EtDs can be used to adopt, adapt or newly develop recommendations.

Secretariat members can extract information from existing guidelines of other organizations (that have been rated as acceptable with the AGREE II instrument, respectively) or systematic reviews (that have been rated as acceptable with the ROBIS) to complete these sections in the EtD or use existing EtDs of other organizations[21]. Information from different organizations can be utilized to complete the EtDs and be summarized into one version when there are recommendations from different organizations. This is particularly important when there are discrepancies in recommendations across guidelines, which need to be resolved through use of a group process based on the EtDs. Evaluating existing recommendations by working through an EtD will allow adaptation or de novo development of guidelines.

The GRADE handbook on the website www.gradepro.org includes the instructions for developing GRADE evidence profiles and for assessing the quality of evidence and developing recommendations. A brief over view of the GRADE approach is provided below. For further information, please use the website www.gradepro.org.

4.1 Using GRADE

The GRADE approach has two main steps: 1) evaluation of the quality of evidence and the preparation of GRADE summary tables and 2) developing recommendations.

4.1.1. Evaluation of the quality of evidence

Quality or certainty in the evidence is defined as the "extent to which one can be confident that an estimate of effect or association is correct". It is a continuum; any discrete categorization involves some degree of arbitrariness. It is based on the following criteria:

[21] http://dbep.gradepro.org/

- risk of bias across included studies. This is also called study design and any limitations of the studies, in terms of their conduct and analysis;
- inconsistency of the results across the available studies;
- imprecision of the results (wide or narrow confidence intervals);
- indirectness (transferability, applicability, generalizability or external validity) of the evidence with respect to the populations, interventions, and settings where the proposed intervention may be used;
- the likelihood of publication bias.

And additionally for observational studies:

- the magnitude of the effect;
- presence or absence of a dose response gradient;
- direction of plausible biases.

'Quality' of evidence is categorized as *high, moderate, low or very low* and the definitions are shown below.

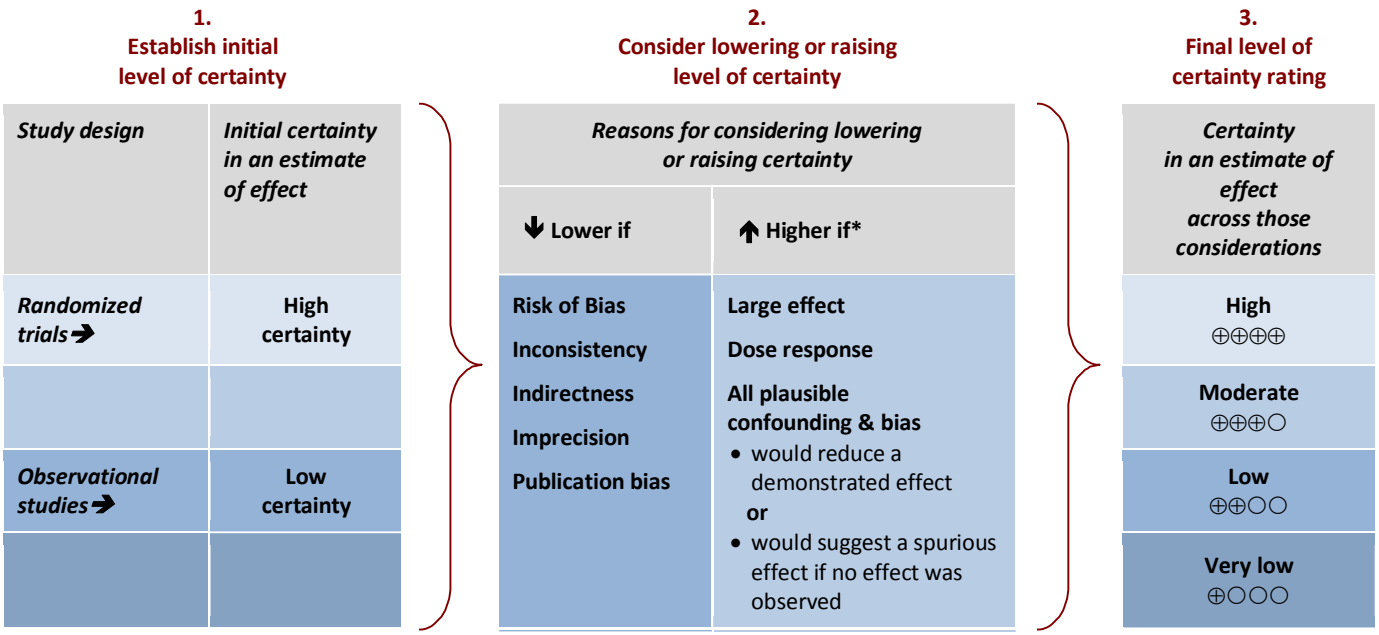
Table 6: Categories of Quality of or certainty in the evidence and their definitions

Ratings	Definitions
⊕⊕⊕⊕ High certainty	The panel is very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯ Moderate certainty	The panel is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯ Low certainty	The panel's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯ Very low certainty	The panel has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The assessment of quality of evidence is carried out automatically in the GRADEpro software.

The criteria for the rating process are summarized in the table below.

Table 7: GRADE quality of evidence: assessment criteria[22]



*upgrading criteria are usually applicable to observational studies only.

Adapted from "Methodological idiosyncracies, frameworks and challenges of non-pharmaceutical and non-technical treatment interventions" (Schünemann 2013)

4.1.2. Preparation of a summary of findings

A summary of findings showing the results of the systematic review (and studies), using both relative and absolute measures, should be prepared.

Summary of Findings and Evidence Profiles are tables constructed by 'rows' for each outcome. There should be at least one table per question and, to make the Table more informative and readable, beneficial outcomes should be separated from harms/side-effects.

To complete the GRADE table, including the Summary of Findings:

- In the first row, fill in the most important beneficial outcome.
- Identify the systematic review(s) that include studies reporting the relevant outcomes.

Not all studies in the reviews may report the outcome of interest and not all outcomes of interest are measured in studies. For each outcome, data should be presented from the subset of studies in the review that reported it or it should be indicated if no study reported or measured it.

[22] GRADE Working Group, http://www.gradeworkinggroup.org.

Fill in the column, 'number of studies'. This is the number of studies in the review that report the outcome. For future reference and checking, it is suggested that these studies are listed as a footnote to the table.

Complete the quality of evidence assessment for these studies, as required in GRADEpro (www.gradepro.org). To complete the Summary of Findings screen:

- extract summary results for relative and absolute measures of effect or where continuous outcomes are reported, the summary estimate of effect (weighted mean difference or standardized mean difference, and variance).

The following information is needed for dichotomous outcomes:

- total number of patients in each group;
- total number with event;
- an estimate of the control group risk (control event rate);
- effect size (relative risks or odds ratios, absolute differences and 95%CIs).

For continuous outcomes the following information is needed:

- total number of patients in each group;
- summary estimate of effect (weighted mean difference or standardized mean difference) and 95% confidence interval.

It is advisable that one reviewer extracts data from the systematic reviews and/or from single studies and prepares drafts of the GRADE tables with detailed footnotes explaining the judgments that were made. Each judgment should be made explicit and available to the reader in order to increase the transparency of the whole process. These should be checked by at least one other member of the Secretariat.

4.1.3 GRADE Evidence to Decision frameworks

The goal of EtD frameworks is to help guideline panels use evidence in a structured and transparent way to inform decisions in the context of clinical recommendations, coverage decisions, and health system or public health recommendations and decisions. The frameworks have a common structure that includes formulation of the question, an assessment of the evidence, and drawing conclusions, though there are some differences between frameworks for each type of decision. They can be adapted for the context and interactive versions are available through GRADEpro. EtD frameworks provide a systematic and transparent approach for going from evidence to healthcare decisions. EtD

frameworks inform panel members and users of the recommendations about the judgments that were made and the evidence supporting those judgments by making the basis for decisions transparent to target audiences. EtDs also facilitate dissemination of recommendations and enable decision-makers.

4.2 Presenting the evidence to the Panel

Insert evidence summaries in GRADE EtD. Draft GRADE EtD frameworks that include GRADE tables, and a draft assessment of resources, values and preferences, feasibility, acceptability and equity should be sent to the members of the panel before the meeting. Panel members should be asked to identify any relevant evidence that is missing from the EtDs. The final summaries are then used as the basis for drafting recommendations. A template for presenting this information is in Appendix 3b.

5 Assessing cost and resource implications

In addition to the clinical evidence, the costs and resource use of preventive, diagnostic, and management strategies have to be taken into account by the guideline panel as they develop guideline recommendations. For this purpose, cost analyses include both budget impact assessment and economic evaluation.

If a guideline recommendation is for interventions that are not already included in the health care services list financed by EHIF and the reimbursed pharmaceuticals list, an application for inclusion of the intervention, including economic evaluation, should be done according to the procedures set out in the legislation.[23] This evaluation should be coordinated with the guideline development process, if possible, to avoid duplication of processes. A parallel process is coordinated by EHIF.

5.1 Formal economic evaluation including cost-effectiveness assessment

It is expected that the majority of recommendations will be developed based on the cost information from the budget impact analysis. An informal assessment will be made using the principles of cost-minimisation. However, if an unbiased estimate of effectiveness for a new intervention shows that it is clinically superior to the existing alternative, a cost -effectiveness analysis may be helpful for developing the final recommendations.

Cost-effectiveness analyses must be done selectively. The first step should be a review to identify any existing economic studies that are relevant. If a full economic evaluation of cost-effectiveness is conducted, it has to take into account the costs and health outcomes (effects) of an intervention assessed in relation to its comparator, and must present an incremental cost-effectiveness ratio (ICER). Effectiveness measures can be units (e.g. disease episodes or deaths prevented), two-dimensional quality-adjusted life years (QALYs) in a cost-utility analysis, or can be expressed in monetary terms in a cost-benefit analysis. Cost-effectiveness analyses often use decision-analytic methods in order to combine evidence from different sources and to extrapolate from the limited time-horizons of existing studies on health outcomes. Once the cost-effectiveness of an intervention is established, an evaluation should be made as to whether the intervention represents value for money and is affordable.

[23] Estonian Health Insurance Fund for health services and their evaluation criteria for amending the list of conditions and procedures (Eesti Haigekassa tervishoiuteenuste loetelu muutmise kriteeriumid ning nende hindamise tingimused ja kord). See: https://www.riigiteataja.ee/akt/122072011010?leiaKehtiv. Also, Estonian Health Insurance Fund and the procedures for amending the listing of medicines and the establishment of a list of criteria for content and compliance with the criteria reviewers (Eesti Haigekassa ravimite loetelu koostamise ja muutmise kord ning loetelu kehtestamise kriteeriumide sisu ja kriteeriumidele vastavuse hindajad). See: https://www.riigiteataja.ee/akt/115052014012?leiaKehtiv.

5.2 Budget impact assessment

The Panel needs to evaluate the budget impact of potential changes in current clinical practice standards that may result from each recommendation. Consideration of cost implications should also be assessed when moving from evidence to recommendations. Generally, all important resource use associated with the recommendation for the new intervention and the comparators are assessed.

After defining the final scope of the guideline, the Panel needs to decide which recommendations are most likely to require consideration of costs and resource use in detail including those for which a formal economic evaluation may be required as well as the budget impact analysis. Complete resource section in EtD frameworks (Appendix 3b) The first step is a summary of budget impact analysis for all initial recommendations by describing alternatives.

This analysis has three steps, namely:

- identification (what type of resource use is associated with the recommendation?)
- measurement (how much of this is used?)
- monetary valuation (what does it cost?)

The description of resource use and costs should be made from the perspective of the health system by identifying the main resources required to implement a specific recommendation. It is important to include resource use associated with the provision of the intervention, subsequent investigations and care, and adverse effects. Implications not only for EHIF but also for other stakeholders (hospitals, etc.) should be taken into account. These should be grouped as costs incurred by the patient, the health system, and society. Those incurred by the patient and health system should always be described (e.g. drug, admissions, visits, examinations). Other resources, such as patient and care-giver time, should generally be considered only when they are deemed to be very important in that context as they are difficult to measure and to put a value on reliably. It is also important to define the time horizon for inclusion of resource use; in other words, when are important differences in resource use likely to occur (in the short-term or the long-term)?

Once resource use is measured, a range of monetary values can be estimated for each item of resource use. For reporting on this costing exercise, it is important not just to document the aggregate costs (number of units of resource use x unit costs of resource) associated with an intervention, but also to report, as far as possible, disaggregated costing information (i.e. all the associated resource use and unit costs separately).

The EHIF, in collaboration with the Secretariat, will prepare the budget impact analysis. If possible, the analysis should include *best case* and *worst case* scenarios, based on existing information about use of interventions and

conservative assumptions about likely changes in the pattern of use following a recommendation. The analyses should be provided to the Panel for evaluation in conjunction with the clinical evidence.

5.3 Taking account of costs in developing recommendations

After clinical evidence, costs are the second criteria considered by the Panel when developing the final recommendation. It is expected that 'strong' recommendations (Chapter II-6: Developing recommendations) will only be made in cases where the intervention or pharmaceutical is affordable in Estonia or accepted for financing by EHIF or some other state agency.

Insert the information of costs to the EtD framework table (use: Appendix 3b).

6. Developing recommendations

6.1 Draft recommendations

Draft recommendations are prepared by the Secretariat and final recommendations must be approved by the Panel.

Use EtD Framework for recommendations.

See Chapter I: Guideline development bodies, for further information on the Panel. A Guideline Panel may need to hold several meetings over the course of 24 months. The duration of the meeting will depend on the content of the guideline, the complexity of the topic, and how many members can attend. Options may include a one-day meeting once per month, or several days every two months, or any length and period of time as deemed necessary. The Chair and panelists should determine the date, frequency and length of meetings together. Ultimately, the purpose of any meetings is to draft or review the guideline and its recommendations.

For each recommendation, the quality of evidence must be presented and information about costs, values and preferences, and feasibility, using the table in Appendix 3b.

The final recommendations should specify the perspective that is taken (e.g., individual patient, health-care system, or society) and which outcomes were considered (including costs, if assessed). Strong recommendations will only be made if an intervention is affordable for Estonia. The language used in recommendations should be clear and direct, indicating an unambiguous action (e.g., all patients with disease *A* should be offered treatment *B* by health professionals).

The language should be consistent across recommendations. For example, all strong recommendations ought to be phrased with “should”.

The strength and quality of recommendation should be indicated in every recommendation (refer to table 7).

6.2 Process of deciding on recommendations by the panel

The panel should reach recommendations based on consensus. Consensus does not necessarily mean unanimity, however, and in some cases, at the discretion of the Chair, a vote may need to be taken. Voting may then be used as a tool to work towards consensus. Panel members collaborate with the Chair to achieve the wording for final recommendations.

The Panel should discuss and agree on the process at the beginning of the meeting. (For information on voting and reaching consensus, see Chapter I-2.5 *Panel meetings*). Interactive Evidence to Decision tool can be used[24].

[24] http://www.decide-collaboration.eu/ietd-interactive-evidence-decision-tool

It is most effective if the Panel considers draft recommendations that have been prepared by the Secretariat as follows:

- start by clearly introducing the question
- the evidence is reviewed and discussed by the panel, considering the balance of evidence for benefits and harms;
- the panel considers costs, as presented by health economists of the Secretariat, to include resource and use costs, budget impact, and possibly cost-effectiveness, along with values and preferences;
- the draft recommendations are presented by the Secretariat, with a justification and reference to the relevant evidence (evaluated by GRADE) summary;
- if necessary, the first recommendation is modified;
- final agreement on the recommendation is reached.

6.3 Grading strength of recommendations

The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to the recommendation will outweigh the undesirable effects.

Desirable effects can include beneficial health outcomes, less burden, and greater savings. Undesirable effects can include harms and increased costs. Burden here refers to the demands of adhering to a recommendation that patients or care-givers (e.g., family members) may find onerous, such as undergoing more frequent tests or opting for a treatment that may require a longer recovery time.

The GRADE system defines two categories of recommendation – strong and weak (also known as “conditional”). A strong recommendation is one in which the guideline development group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This can be either in favour of or against an intervention. A weak recommendation is one in which the panel concludes that the desirable effects of adherence probably outweigh the undesirable effects, but the group is not confident about the trade-off.

Reasons for not being confident may include:

- ✓ absence of high-quality evidence;
- ✓ presence of imprecise estimates of benefit or harm;
- ✓ uncertainty or variation in how different individuals value the outcomes;
- ✓ small benefits;
- ✓ benefits that are not worth the costs (including the costs of implementing the recommendation).

Despite the lack of a precise threshold for moving from a strong to a weak (conditional) recommendation, the presence of important concerns about one or more of the above factors make a weak recommendation more likely (Table 8). The Guideline Panel should consider all these factors and make the reasons for their judgments explicit. It is expected that 'strong' recommendations (Chapter II-6: Developing recommendations) will only be made in cases where the intervention or pharmaceutical is affordable in Estonia or accepted for financing by EHIF or some other state agency.

Implications of a strong recommendation are:

- **For patients**: Most people in their situation would want the recommended course of action and only a small proportion would not.
- **For clinicians**: Most patients should receive the recommended course of action. Adherence to this recommendation is a reasonable measure of good-quality care.
- **For policy-makers**: The recommendation can be adapted as a policy in most situations. Quality initiatives could use this recommendation to measure variations in quality.

Implications of a conditional recommendation are:

- **For patients**: The majority of people in their situation would want the recommended course of action, but some would not.
- **For clinicians**: Be prepared to help patients to make a decision that is consistent with their own values.
- **For policy-makers**: There is a need for substantial debate and involvement of stakeholders.

Table 8: Factors that may influence the strength of recommendations[25]

Factor	**Examples of strong recommendations**	**Examples of weak (conditional) recommendations**
Quality of evidence	Many high-quality randomized trials have demonstrated the benefit of inhaled steroids in asthma	Only case series have examined the utility of pleurodesis in pneumothorax

[25] GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, Oxman AD, et al. BMJ, 26 April 2008, 336:924-926. Available at: http://www.gradeworkinggroup.org/publications/GRADE-1_BMJ2008.pdf

Uncertainty about the balance between desirable and undesirable effects	Aspirin in myocardial infarction reduces mortality with minimal toxicity, inconvenience, and cost	Warfarin in low-risk patients with atrial fibrillation results in small stroke reduction, but increased risk of bleeding and substantial inconvenience
Uncertainty or variability in values and preferences	Young patients with lymphoma will invariably place a higher value on the life-prolonging effects of chemotherapy over treatment toxicity	Older patients with lymphoma may not place a higher value on the life-prolonging effects of chemotherapy over treatment toxicity
Uncertainty about whether the intervention represents a wise use of resources	The low cost of aspirin as prophylaxis against stroke in patients with transient ischaemic attacks	The high cost of clopidogrel and dipyridamole/aspirin as prophylaxis against stroke in patients with transient ischaemic attacks

Many recommendations are labelled as either *strong* or *weak*. However, because the *weak* label may sometimes be misinterpreted, other options exist. These include the use of terms such as *strong/conditional* or *strong/qualified*.

The wording of recommendations is important. Use consistent language across recommendations. To ensure that end users will understand the specific linguistic and cultural contexts of the wording, sample text should be validated with them. The key to the wording must always be attached to the guideline. Some examples are in the table 9 below.

Table 9: Examples of wording for recommendations

	Wording 1	Wording 2	Wording 3
Strong recommendation for	We recommend…	Clinicians should…	We recommend…
Weak recommendation for	We suggest…	Clinicians might…	We conditionally recommend…
Weak recommendation against	We suggest...not	Clinicians might not…	We conditionally recommend...not

Strong recommendation against	We recommend …not	Clinicians should not…	We recommend …not

6.4 Indicators for implementation

In addition to approving the guideline implementation plan, it is also the responsibility of the GAB to oversee the implementation process. The Panel should approve indicators for monitoring the implementation of the guideline and its impact, based on the final recommendations that are graded as *strong* recommendations. When weak recommendations are selected (ideally only those based on high-quality evidence) the decision-making process (a dyad approach between the patient and the clinician) can function as a quality indicator.

In general, indicators can be *process* indicators (e.g., prescription rates for specific medicines; length of hospital stay), *outcome* indicators, (i.e. readmission to hospital due to a specific cause), or *clinical events* (e.g., patients experiencing myocardial infarction).

The indicators that are prepared by the Secretariat and selected by the Panel should be events or processes that are expected to be affected as a result of the recommendation. In some instances, the indicators may be the same as the critical outcomes used by the Panel in making recommendations. They may also be processes or events that can be measured by use of routine data collected by the EHIF or health-care providers. An alternate method is to carry out audits, which may also contribute to the guideline implementation process. There is no pre-specified number of indicators required for a guideline, but if there are several strong recommendations, there may need to be several indicators.

The final selection of indicators should be done in consultation with the key stakeholder likely to be involved in implementing the guideline and approved by the GAB as a part of the final guideline.

III Patient guidelines

Clinical guidelines are developed on the basis of this manual and approved by the GAB include as well patient guidelines resulting from the clinical guidelines. Patient guidelines are a key component in the implementation of clinical guidelines and aim to improve patient awareness and active cooperation in order to achieve better treatment outcomes. Accordingly, it should be ensured that any recommendations provided in patient guidelines conform to the relevant clinical guideline.

1 Development process of patient guidelines

The patient guidelines is an activity with several phases and teamwork involving various parties. Process is guided by recommendations for the Estonian clinical guideline about to be produced, the basis in evidence of additional information submitted and the general principles for development.

1.1 Planning

Generally, during the process of the production of clinical guidelines the party completing the patient guidelines is the relevant head of the secretariat, involving in developing process any experts recommended by the working group as needed, in addition to patient representatives. Planning the development of patient guidelines begins with planning clinical guidelines.

Along with the completion of initial clinical guideline recommendations, the head of the secretariat submits a list of patient guideline subjects to the working group which assesses the importance of the subjects in the patient guidelines similarly to the methodology for the outcomes for the scope of application of the clinical guidelines (Chapter II-2.5, *Choosing and rating outcomes*). The working group approves those completing the guidelines.

Based on the plan assembled for developing the patient guidelines, the head of the secretariat defines the required resources and obtains advance approval from the sponsor of the clinical and patient guidelines for the timeline for their finalizing (will be completed within an estimated 3 months from the approval of the clinical guidelines by the GAB).

1.2 Development and approval phases

- Patient guidelines are developed in parallel to the development of clinical guideline recommendations.
- During the assembly of preliminary material, it is ensured that material completed clearly conforms to the recommendations in the clinical guideline.
- It is identified what materials on the same subject have been published for patients in Estonia already. If it becomes apparent that recommendations conflicting with them have been published in Estonia, this should be assessed, and, if necessary, contact should be made with the holders of

copyright to those materials in order to prevent any conflicting recommendations being given to patients subsequently.

- If additional recommendations are provided in patient guidelines compared to clinical guidelines, those completing them should verify that the materials are based on evidence. The assessment and documentation of additional evidence is subject to the same rules as apply to the sources used in clinical guidelines.
- Members of the Panel assesses completed guidelines, providing an initial assessment of and feedback on their content and wording.
- Guideline initially developed and assessed by the working group should undergo testing in a patient focus group including representatives of the target group. It is advisable to recruit for the focus group people with various social and educational backgrounds, in order to identify any queries. Testing is organised by the sponsor of the patient guideline and observed by the head of the patient guideline secretariat, in addition to the sponsor.
- In parallel, information on patient guidelines is provided to the appropriate existing patient associations in order to obtain an assessment.
- The head of the secretariat documents, assesses and coordinates feedback on completed patient guidelines received from focus groups or any other stakeholders and submits it to the working group, who will form a position along with reasoned proposals on whether to take any suggestions for improvement into account or not.
- All proposals must reviewed and changes must be approved by the Panel.

Patient guidelines are approved by the GAB, to which the preliminary printed version of the patient guideline, designed and edited, is submitted. Patient guideline documentation submitted consists of the absence of any contradiction between the relevant clinical guideline and patient guideline, as confirmed by the working group. Appended to the materials are a summary of feedback from the patient focus group and the clinical guideline implementation plan with respect to the patient guideline implementation plan.

1.3 Structure of patient guidelines

The format and design of patient guidelines has been agreed and is partly similar to those of clinical guidelines. The structure of patient guidelines derives from the specific guidelines but contains information on the preparation for a procedure/investigations, the illness and the course and prognosis thereof, treatment, follow-up, and self-help measures. The text is readily readable and can be understood by people with various backgrounds. It is advisable that the content of patient guidelines should not exceed 20 pages.

Documents on patient guidelines, including the completion of guidelines, are published and disseminated on the same basis as clinical guidelines (Chapter V of the current manual).

1.4 Assessment of the effectiveness of patient guidelines

A year after the dissemination of a patient guideline, the sponsor of the patient guideline will arrange a representative feedback study, as indicated in the implementation plan, in order to assess the effectiveness of the guidance material. Every guideline user can provide direct feedback on the ravijuhend.ee site. The feedback contact available on the site is noted in the patient guideline. The procedure for updating patient guidelines is similar to that for updating clinical guidelines.

IV Clinical Pathways

Both clinical guidelines and clinical pathways aim to improve care quality for patients. In the process of the completion of clinical guidelines, schematic clinical pathways may be also produced as part of clinical guidelines. Sometimes, however, it may be more efficient and less time-consuming compared to clinical guidelines to present clinical pathways for patients in the form of algorithms only, not always preceded by the completion of clinical guidelines, in order to improve care quality for patients. Nevertheless, both in this case and in case of guidelines taken over from international clinical pathways, the principles (search, assessment, documentation of sources etc.) set out in the Estonian manual on the completion of clinical guidelines for obtaining approval by the GAB for guidelines apply.

For the purposes of this manual, clinical pathways are consolidated information, or step by step codes of conduct in the form of drawings (algorithms), containing consecutive actions, stipulated over a time period and agreed for a precisely defined patient group on specific bases in evidence, that are connected to the making of shared decisions by various parties in the health care system, to investigations and to treatment as well as to the provision of other related services for the patient [26].

Clinical pathways set out clearly the purpose and key elements of an action (diagnosis, treatment or the like), taking into account the best practice, patients' expectations and the national health care set-up. An important role is played by the coordination of the treatment process, which specifies the roles of the multidisciplinary team, the patient and those close to her/him as well as the sequence of actions. Actions indicated in clinical pathways are allocated among various health care levels to various treatment phases. In addition to the movement of a patient among various treatment phases, clinical pathways also establish the procedure for documenting, assessing and reporting in case of the relevant patient among various parties in health care.

1. Development process of Clinical Pathways

As an evidence based standard (including the relevant literature, applicable clinical guidelines and best practice, clinical pathways ensure the comprehensive handling of a patient, regardless of the initial point of contact, from a diagnostic hypothesis through to treatment / care outcomes. Given the documented communication and assessment process among various parties, compliance with the standard is monitored, enabling feedback to be obtained from the parties.

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[26] Vanhaecht, K., De Witte, K. Sermeus, W. (2007). The impact of clinical pathways on the organisation of care processes. PhD dissertation KULeuven, 154 pp, Katholieke Universiteit Leuven

In order for the completion of a clinical pathway to be approved by the GAB, a reasoned subject initiative, similarly to the initiative for the subject of a clinical guideline, may be submitted (Chapter II-1: Topic proposal and selection). Clinical pathway subject initiatives may be submitted similar to the Clinical guidelines by 1 February. The GAB will consider the proposals during its next regular meeting. The GAB assesses initiatives, approving or rejecting them.

A subjective initiatives clearly states:

- the objective;
- who the clinical pathway is aimed at;
- the reason (for example, evidence based literature, patient expectations or the national health care set-up);
- presumed impact on the health care set-up;
- an explanation why a clinical pathway, rather than a clinical guideline is the more appropriate way;
- the envisaged implementation plan.

If a clinical pathway subject initiative is approved, a clinical pathway secretariat is formed, subject to the requirements set for a clinical guideline secretariat in this manual (Chapter I-3, *Secretariat*). Members of the secretariat are required to submit declarations of interest (Appendix 1).

In completing clinical pathways, the secretariat draws on evidence based sources published along with the clinical pathways at least electronically. Equally evidence based recommendations are provided taking into account the results of the assessment of the cost-effectiveness of each recommendation. Actions are described taking into account the local health care set-up.

In the process of the completion of clinical pathways, meetings of the secretariat are minuted similarly to the operating principles for the completion of clinical guidelines (Chapter I-3.5, *Secretariat meetings*), setting out the reasoning and decisions of the secretariat as well as the sources on which the decisions are based. Minutes of the meetings of the secretariat are published electronically on the ravijuhend.ee site as part of the process of the completion of clinical pathways. Based on evidence and the decisions and reasoning of the secretariat, clinical pathways or clinical pathway algorithms are completed. A sample of the structure of clinical pathways is attached (Annex 11, *Clinical pathway for patients diagnosed with cervical cancer*).

Preliminary clinical pathways are submitted for public assessment and commented on by the appropriate professional association via the www.ravijuhend.ee web application. The secretariat discusses and assesses any comments and suggestions for improvement received during a public consultation within a reasonable time period. Concerning every comment or suggestion for improvement received, the secretariat will provide feedback in

writing as to whether it is to be taken into account or not, with the feedback published on the ravijuhend.ee site.

2. Approval of Clinical Pathways

The approval of clinical pathways is similar to the approval of clinical guidelines by the GAB. The final versions of clinical pathways together with the implementation plans are submitted to the GAB by the secretariat, which also provides information about the comments and suggestions for improvement received during the public consultation.

V Implementation

1. Publication and dissemination

All documents used and developed during the guideline development process will be saved and stored in a unique electronic environment with limited public access.

Publicly available, printable documents will be available on special website (http://www.ravijuhend.ee) will include:

- The full Guideline document (max 20 pages + appendixes)
- A shorter Guideline version (1-2 pages)

Appendixes of guidelines are:

- Algorithm (approximately one A4)
- Evidence summary (see Appendix 3b)
- Short overview of development process with Panel and Secretariat incorporating minutes from the meetings and declaration of interests.

The algorithm and the short version of the guideline will also be available in a user-friendly, printable Adobe PDF-version and delivered based on a distribution plan. If the initiator suggested and GAB approved the full guideline document, it will be published and delivered as indicated in the plan.

2. Guideline implementation

Successful implementation of the guideline depends on the effectiveness of the implementation process and its awareness and acceptance by related health-care professionals, patients, and civil servants.

The Implementation Plan prepared by the Secretariat and approved by the Panel should be added to the final guideline and presented to GAB for acceptance.

In developing the Implementation Plan, the different issues should be considered to ensure the dissemination and implementation of the guideline within a reasonable time period, including measurement and evaluation systems and necessary resources. The implementation process might be divided into several stages, if this is needed, due to local circumstances or other essential reasons. See the Guideline implementation planning checklist[27]

In developing the Implementation Plan, the following key issues should be considered:

1. **Identify potential barriers** and develop a plan to deal with them. **Define success criteria and respective indicators** to measure successful implementation.

[27] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329197/

2. **Measure the baseline data for established indicators**. Ensure that data is collected which accurately reflects the current situation and provides the baseline for monitoring and auditing progress in the future.
3. **Identify resources needed**. Resources required, including financing, personnel and time, should be clearly outlined in the Implementation Plan.
4. **Identify the need for training and education** and include necessary activities in the Implementation Plan (example: regular trainings, E-lectures, webinars).
5. **Think out information management**. Decide how to get relevant information to stakeholders and identify individuals to collate and disseminate information relating to the guideline.
6. **Use existing mechanisms/networks** for implementation rather than establishing new ones. Ensure that the action plan is coordinated through existing clinical governance framework. Include guidance implementation in **performance management systems**, if possible.
7. **Determine methods for monitoring the implementation process**; a regular evaluation system should be set. Use electronic tools for implementation (for example apps). **Define feedback** and reporting of implementation to the GAB after a predefined time period.
8. Determine clear roles and responsibilities for each action.
9. **Determine milestones with timescales** for each stage of the implementation process.

A template for the Implementation Plan is in Appendix 8.

VI Updating a guideline

The prepared guideline should generally be updated five years after publication. Updating should be considered routinely one year earlier when EHIB will present to GAB a list of potential updated guidelines. GAB will estimate the need by assessing appropriate statistics, audits, opinion of stakeholders.

Guideline needs updated every time, if important new evidence becomes available that might change the content of the recommendations, or if there are important organizational changes in the health-care system that result in a need to revise the recommendations and/or the results of a guideline implementation assessment show the need to review recommendations.

Updating a guideline may include a change of scope — not only in the questions, but also in the selection of critical outcomes, which may differ from the existing guideline.

The guideline updating process follows the same process as the general guideline development process. When updating the guideline, use existing evidence tables and update those.

VII Glossary and acronyms

Algorithm: in this context, a flow chart or decision tree to illustrate the choices and recommendations suggested in a clinical practice guideline

Assessment of Multiple Systematic Reviews (AMSTAR) checklist: A list of 11 items used to measure the methodological quality of systematic reviews.

Appraisal of Guidelines for Research and Evaluation (AGREE) instrument: A tool developed through international collaboration that provides a framework for assessing the quality of clinical practice guidelines. See:

http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf.

Agency for Healthcare Research and Quality (AHRQ): Part of the United States' Department of Health and Human Services, tasked with improving the quality, safety, efficiency, and effectiveness of health-care for Americans. AHRQ supports research that helps people make more informed decisions and improves the quality of health-care services. AHRQ was formerly known as the Agency for Health Care Policy and Research. See: http://www.ahrq.gov.

Budget impact analysis: Makes clear what the costs and impacts are if a health intervention is implemented on a national scale. For the analysis to be effective, it is important to know—in addition to investments and possible savings at the level of patients, health-care providers, or practices—how many patients, health-care providers, and practices are eligible for the implementation strategy. Multiplying these two figures can provide policy makers the likely total costs and savings generated by a wide distribution of the implementation strategy.[28]

Canadian Agency for Drugs and Technologies in Health (CADTH): An independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health-care decision makers. See: http://www.cadth.ca.

Case control studies/Case series: Studies or a report on a single patient in which patients who already have a specific condition are compared with people who do not. They often rely on medical records and patient recall for data

[28] Grol R, Wensing M, and Eccles M, Improving Patient Care: The Implementation of Change in Clinical Practice. Elsevier Butterworth Heinemann, Edinburgh, 2005, 283.

collection. These types of studies are less reliable than randomized controlled trials and cohort studies, because showing a statistical relationship does not mean than one factor necessarily caused the other.

Clinical guideline, clinical practice guideline: A document that focuses on a disease or condition and includes recommendations for appropriate treatment and care of patients with this disease or condition. The guideline should be based on the best available evidence and should help health-care providers by supplementing their knowledge and skills.

Clinical question/key question: A question that is formulated using the PICO framework, wherein the health-care provider asks and answers a series of questions meant to elicit information about their patient and their condition, interventions that have been undertaken or should be taken, any comparisons between the current treatment and possible alternatives, and outcomes to be desired or achieved. See Section I-2.4 Formulating questions for the scope, Table 1: PICO framework for an example of how to use PICO in formulating clinical or key questions.

Cochrane Collaboration: An international network helping health-care providers, policy makers, patients, and their advocates and care givers make well-informed decisions about human health-care by preparing, updating, and promoting accessibility to Cochrane reviews to provide "the best evidence for health care". See http://www.cochrane.org.

Cohort studies take a large population and follow patients who have a specific condition or receive a particular treatment over time and compare them with another group that has not been affected by the condition or treatment being studied. Cohort studies are observational and not as reliable as randomized controlled studies, since the two groups may differ in ways other than in the variable under study.

Conflicts of interest (COI): According to the World Health Organization, a conflict of interest is "any interest declared by an expert that may affect or reasonably perceived to affect the expert's objectivity and independence in providing advice" on the development of a guideline.

Cost analysis: The analysis of two strategies where the focus is on comparison of costs with regards to resource use and expected outcomes.

Cost implications: The cost consequence that may result from implementing a specific guideline or guidance on health-care.

Cost-benefit analysis: A form of economic analysis in which both the costs and the consequences, including increases in the length and quality of life, are expressed in monetary terms.[29]

Cost-effectiveness: Effective or productive in relation to its cost.

Cost-effectiveness analysis: An economic analysis in which the consequences are expressed in natural units. Some examples would include cost per life saved or cost per unit of blood pressure lowered.[30]

Cost-minimization analysis: An economic analysis conducted in situations where the consequences of the alternatives are identical, and so the only issue is their relative costs.[31]

Cost-utility analysis: A type of cost-effectiveness analysis in which the consequences are expressed in terms of life-years adjusted by peoples' preferences. Typically, one considers the incremental cost per incremental gain in quality adjusted life-years (QALY).[32]

Declaration of interest (DOI): According to the World Health Organization, a declaration of interest is the disclosure of any potential or actual conflicts of interest that include financial, professional, or other interests relevant to the subject of the work or meeting in which an expert may be involved and any interest that could significantly affect the outcome of the meeting or work. The declaration of interest must also include any relevant interests of others who may, or may be perceived to, unduly influence the expert's judgment, such as immediate family members, employers, close professional associates, or any others with whom the expert has a substantial common personal, financial, or professional interest. See http://www.who.int/ipcs/methods/harmonization/areas/mutagenicity_doi.pdf.

[29] User's Guide to the Medical Literature: Essentials of Evidence-Based Clinical Practice. Edited by Guyatt G and Drummond R. Journal of the American Medical Association, 2002, 408.
[30] Ibid.
[31] Ibid.
[32] Ibid.

Dichotomous outcomes: Any outcome measure in which there are two possibilities such as dead/alive, admitted/discharged, pregnant/not pregnant, and where the patient must be in one, but cannot be in both categories.[33]

Economic evaluation: A set of formal, quantitative methods used to compare two or more treatments, programs, or strategies with respect to their resource use and their expected outcomes.[34]

Estonian Health Insurance Fund (EHIF): The national health insurance fund for the country of Estonia. According to the guideline development process, EHIF is a member in all processes and provides administrative support to the guideline development bodies. Additionally, EHIF is a potential financer of guideline development process.

See http://www.haigekassa.ee.eng/ehif.

Evidence retrieval: In the context of systematic reviews and evidence based medicine, the process of systematically searching for all scientific studies that are relevant to a particular question, and obtaining them from libraries or journals to review them

Evidence summary/summary tables: A standard format, usually tables, used to present a concise overview of clinical evidence

Formal consensus: A systematic approach to eliciting agreement from a panel ; described in detail in *Consensus development methods, and their use in clinical guideline development.* (Murphy MK, Black NA, Lamping DL, et al. Health Technol Assess 1998;2(3):i-iv, 1-88. Available at: http://www.hta.ac.uk/fullmono/mon203.pdf.)

Grading of Recommendations Assessment, Development and Evaluation (GRADE) system: A collaborative working group that has developed a common, sensible, and transparent approach to grading quality of evidence and strength of recommendations used by many international organizations. See http://www.gradeworkinggroup.org.

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[33] For additional clarification, see Last J, ed. A Dictionary of Epidemiology, Fourth Edition. Oxford, Oxford University Press, 2001. See also http://www.cochrane-net.org/openlearning/PDF/Module_11.pdf.

[34] Ibid, 411.

Guideline Advisory Board (GAB): The body whose tasks include the annual selection of potential guidelines for development out of proposed topics, and acceptance of the final guideline for approval.

Guideline Panel: Develops and agrees on the recommendations in the guideline and endorses the final guideline document for approval by the GAB. Another important task of the Guideline Panel is to facilitate the implementation of the guideline at country level.

Implementation plan: A plan for the dissemination, measurement, and evaluation of the usefulness of a guideline. The plan should include the identification of potential barriers, criteria and indicators for success, baseline data for established indicators, needed resources, training and education needs, dissemination of information to appropriate stakeholders and users, identification of existing mechanisms or networks, methods for monitoring the implementation process, reporting and feedback mechanisms, and milestones with timescales. See Section V: Implementation and Appendix 10: Template for Implementation Plan.

Incremental cost-effectiveness ratio (ICER): The additional cost of one unit of outcome gained (e.g. a QALY or infection averted) by a health-care intervention or strategy, when compared to the next best alternative, mutually exclusive intervention, or strategy.[35]

Intervention: Evidence-based options for diagnosis and care of patients, including prevention, pharmaceutical treatment, surgical techniques, patient education strategies, and other types of therapeutic choices.

Medical Subject Headings (MeSH): The U.S. National Library of Medicine's vocabulary thesaurus used for indexing articles for PubMed. It consists of sets of terms naming descriptors in a hierarchical structure that permits searching at various levels of specificity. See: http://www.nlm.nih.gov/pubs/factsheets/mesh.html.

National Institute for Health and Clinical Excellence (NICE): A National Health Systems organisation based in London and Manchester, UK. The organisation works to ensure equal access to medical treatments and high quality care from the NHS for citizens in England and Wales. NICE provides guidance,

[35] Incremental cost effectiveness ration, Health Economics Glossary of Terms. At: http://www.healtheconomics.nl/W/Incremental_cost_effectiveness_ratio

sets quality standards, and manages a national database to improve people's health and prevent and treat ill health. See http://www.nice.org.uk

Outcomes: Changes in health status that may occur in following subjects or that may stem from exposure to a causal factor or to a therapeutic intervention.[36]

Peer review: A process of subjecting scholarly works, research, or ideas to the scrutiny of others who are experts in the same field.[37]

Population/Patient-Intervention-Comparison-Outcome (PICO): A mnemonic used to remind health-care providers of the four questions that are most helpful in developing a clinical question and assessing and determining a patient's care. A table outlining PICO can be found in Section 2.4, Table 1: PICO framework.

Quality assessment: See Risk of bias assessment.

Quality-adjusted life years (QALY): The number of years of expected life corrected for the quality of life that patients are expected to experience in those years.[38]

Randomized controlled clinical trials: Carefully planned projects that study the effect of a therapy on real patients. They include methodologies that reduce the potential for bias (randomization and blinding) and that allow for comparison between intervention groups and control groups (no intervention).

Recommendation: A course of action recommended by the guideline based on clinical questions and evidence retrieval.

Risk of bias assessment: A systematic assessment of characteristics of the design and conduct of clinical trials that have been shown to result in bias in the results, i.e. estimates of the effect that are not accurate. Also called 'quality assessment' of clinical trials. See the Cochrane Handbook for full details.

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[36] User's Guide to the Medical Literature: Essentials of Evidence-Based Clinical Practice. Edited by Guyatt G and Drummond R. Journal of the American Medical Association, 2002, 419.

[37] Peer review: benefits, perceptions and alternatives. Ware M., Mark Ware Consulting. Publishing Research Consortium, London, 2008, 6. See: http://www.publishingresearch.net/documents/PRCsummary4Warefinal.pdf.

[38] User's Guide to the Medical Literature: Essentials of Evidence-Based Clinical Practice. Edited by Guyatt G and Drummond R. Journal of the American Medical Association, 2002, 424.

Scope: The scope provides the framework within which to conduct the guideline development work. Aspects that the scope should define include: Population to be included or excluded; health-care settings; types of interventions and treatments to be included or excluded; information and support for patients and care-givers; outcomes to be considered; and links with other relevant guidance.

Secretariat: A group of individuals tasked with supporting the Guideline Advisory Board (GAB) and the Guideline Panel(s) in preparing for the development and writing of the guideline. The Secretariat provides technical support and research assistance, as well as administrative support.

Stakeholder: Parties or users who are interested in the content of or the outcome of a guideline. This may include health-care providers, patients, patients' families, care-givers, medical and/or nursing associations, experts in a disease or condition, research institutions, and policy-makers.

Systematic reviews: A review that usually focuses on a clinical topic and answers a specific question. An extensive literature search is conducted to identify all studies with sound methodology. The studies are reviewed and assessed, and the results are summarized according to the predetermined criteria of the review question.

Topic: A topic specifies the disease or condition that will be covered by the guideline, as well as the target population and setting in which the care will be delivered.

World Health Organization (WHO): The directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends. See http://www.who.int/about/en.

Appendices

Appendix 1 Declaration of interests

Appendix 2 Panel chair's checklist

Appendix 3a Template of Evidence profile

Appendix 3b Evidence to recommendation table

Appendix 4 Search strategy example

Appendix 5a Table format for mapping guidelines to scope questions

Appendix 5b Summary tables of recommendations of guidelines

Appendix 6 Template for search strategy

Appendix 7a Summary of studies table

Appendix 7b ROBIS instrument

Appendix 8 Template for implementation plan

Appendix 9 Template for topic proposal

Appendix 10a Template for scope

Appendix 10b Rating table for outcomes

Appendix 11 The Clinical Pathways

Appendix 1 Form for the declaration of private interests

A person who is sufficiently qualified to act as an expert may have private interests related to their field of expertise. At the same time, it is essential to avoid situations in which such interests may adversely affect the impartiality of the expert or the result of the work with which he or she is associated.

To ensure transparency of the experts on drafting the clinical guidelines, and thus secure the trust of the public towards the work, the experts acting in a consultative role must disclose any facts which might be the cause of a **potential conflict of interest** (i.e., any interest that may influence the expert's objectivity and independence or which it could be reasonably expected to affect the objectivity and independence of the expert).

In this declaration of interests, you will be asked to disclose any financial, professional or other interests that are important in terms of your participation or the subject matter of the meeting, and any interest that the outcome of the meeting or the work may significantly affect. Also, you will be asked to declare the relevant interests of other parties, who may, or in the case of whom it is thought that they may adversely affect your decision, such as close family members, employers, close co-workers or other persons with whom you have substantial common personal, financial or professional interests.

We ask you to give consent to the effect that any major conflicts may be **disclosed** to other participants in the meeting and presented in the minutes of the meeting or in any other work outcome. If there are doubts about the objectivity of the work or a meeting with your participation or if it is found that the disclosure is made in the best interest, the information disclosed by you **may,** after discussing the issue with you, be **disclosed** to third parties at a later time.

Name:

Authority:

E-mail:

The date of the meeting or the work:

The title of the meeting, including a description of the subject matter (if substances or processes are assessed, a list thereof must be added):

The interest to be declared	***Yes/No***	***In case of a "Yes" list all the related companies and organizations***
EMPLOYMENT RELATIONSHIP AND COUNSELING		
*Have you **in the last two years,** received a fee from businesses or any other organization who is interested in the field covered in the meeting or in the work?* ***Please also inform of any future work related activities or negotiations***	☐ *Yes* ☐ *No*	
RESEARCH GRANT		
*Has your department or research unit **in the last two years,** received support or financing from businesses or any other organization who is interested in the field covered in the meeting or in the work? Please also inform of any future applications or allocation of a research grant.*	☐ *Yes* ☐ *No*	

INTELLECTUAL PROPERTY		
Do you currently have intellectual property rights that may expand or be restricted as a result of the meeting or the work?	☐ *Yes* ☐ *No*	
PUBLIC VIEWS AND POSITIONS		
Have you, during the last two years, been holding a paid or unpaid office; or worked in any other profession in which you are expected to represent or defend a position related to the subject matter of the meeting or a position related to the field of the work?	☐ *Yes* ☐ *No*	
ADDITIONAL INFORMATION		
According to your knowledge, will the result of the meeting or the work benefit the people with whom you have shared important personal, financial or professional interests, or adversely affect their interests? (Under such persons are meant your adult children or brothers and sisters, close colleagues, administrative unit or department.)	☐ *Yes* ☐ *No*	

<u>DECLARATION</u>. I hereby declare that the disclosed information is to my knowledge correct and complete.

Should the above information change due to my new interests, I will notify thereof to the parties concerned and will fill a new declaration of interests, describing the changes. Such changes will be all the changes that occur before the meeting or the start of the work, or during them up to the time of final publication of the results.

Date: _____ Signature:
_____

Appendix 2 Panel chair's checklist [39]

Checklist for Guideline Panel Chairs©
Meeting nr ……. | YYYY/MM/DD
Name of meeting:

Before the meeting

- ☐ Ensure involvement of panel members in the question (PICO) development process
- ☐ Familiarize yourself:
  - ☐ with all material
  - ☐ with the strategies for declaring and managing COI
  - ☐ with panelists and their declared COI
  - ☐ with controversial issues
- ☐ Ensure background material (i.e., particularly, systematic reviews and evidence profiles) is disseminated to panel members ahead of time
- ☐ Ensure meeting worksheets (i.e., evidence to recommendation/decision frameworks, including neutral recommendations) are ready for the meeting
- ☐ Allow for sufficient face-to-face meeting time with the technical team (systematic reviewers and guideline methodologists) before the meeting starts

At the beginning of the meeting

- ☐ Introductions
- ☐ Make appropriate acknowledgments
- ☐ As people introduce themselves, note names and seating of panelists
- ☐ Solicit any new COI since they were last declared
- ☐ Remind panelists about the confidentiality of discussions
- ☐ Clarify ground rules (rules of process)
- ☐ Stress importance of adhering to methodology and that "this is not the time to discuss its value"
- ☐ Clarify who is a voting panelist and who is not
- ☐ Review goals and agenda and stress importance of adhering to schedule
- ☐ Check if panel members are representing organizations

Throughout the meeting

- ☐ Structure the discussion around the decision tables (and the factors that affect the final recommendation)
- ☐ As panelists raise points that are relevant but not directly related to factors that not directly affect the recommendation, attempt to classify them as: conditions/key remarks to go underneath the recommendation statement; implementation considerations; monitoring considerations; implications for future research
- ☐ Offer a neutral recommendation as a starting point for discussing the recommendation statement
- ☐ Discuss first the direction of the recommendation (for vs. against) then its strength (strong vs. conditional)
- ☐ In trying to achieve consensus among panelists:
  - ☐ Check first whether there is agreement.
  - ☐ If not, label the disagreement; clarify what people are agreeing on and what they are disagreeing on; and check whether those disagreeing would be willing to accept the majority's opinion.

[39] Schünemann and Akl, McMaster University 2013

- If not, ask whether a modification or addition would make them agreeable.
- If not, resort to voting.

- ☐ Enforce time, assign someone to help with time keeping if needed
- ☐ Enforce the COI management strategy
- ☐ Stay alert to, and manage strong advocacy
- ☐ Note to minute taker important points to go in the meeting report or guideline document; this is particularly relevant when you need to ensure transparency
- ☐ Clarify conceptual issues as needed
- ☐ Ensure everyone has the chance to participate, particularly community/patient representative
- ☐ Allow for time to debrief with the technical team during the meeting at regular intervals and as needed

At the end of the meeting

- ☐ Summarize what has been achieved
- ☐ Agree on what needs to be achieved after the meeting
- ☐ Clarify communication plan
- ☐ Make appropriate acknowledgments

Appendix 3a Template of Evidence profile

Author(s): WHO Expert Group on Bedaquiline for MDR-TB
Date: 2013-01-30
Question: *In MDR-TB patients, does the addition of a bedaquiline to a background regimen based on WHO recommendation safely improve patient outcomes ?*
Bibliography: 1. Janssen Pharmaceutical Companies. 2012. TMC207 (bedaquiline) treatment of patients with MDR-TB (NDA 204-384). Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 (document available for public disclosure without redaction). 2. FDA AIDAC Meeting 28 Nov 2012. Slide presentations by Janssen R&D; Slide presentations by FDA staff.(http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm)
Definitions of study population:
ITT = intention to treat population (all randomised subjects who had received at least one dose of treatment); conventionally used to assess safety parameters in drug trials;
mITT = modified intention to treat population (all missing or discontinued subjects are regarded as failures); conventionally used to assess efficacy parameters in drug trials

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to SLBR	SLBR alone	Relative (95%CI)	Absolute		
Subjects Cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]												
1[3]	randomised trials	no serious risk of bias[4]	no serious inconsistency	serious[3]	serious[3]	none	38/66[1] (57.6%)	21/66[1] (31.8%)	RR 1.81 (1.26 to 2.31)[3,6]	26 more per 100 (from 8 more to 42 more)	⊕⊕OO LOW	CRITICAL
Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) [7] **(assessed through clinical and laboratory results)**												
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	Serious[9]	very serious[5]	none	7/102[10] (6.9%)	2/105 (1.9%)	RR 3.6 (0.77 to 14.00)	5 more per 100 (from 0 to 25 more)	⊕OOO VERY LOW	CRITICAL
Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)												
1[11]	randomised trials	no serious risk of bias	no serious inconsistency	serious[12]	very serious[3]	none	9/79[11] (12.7%)	1/81[11] (2.5%)	RR 9.23 (1.20 to 72.95)[13,14]	10 more per 100 (from 0 more to 53 more)	⊕OOO VERY LOW	CRITICAL
Time to conversion over 24 weeks (C208 Stage 2: mITT[1]) (measured with microbiological endpoints - MGIT960)												
1[15]	randomised trials	no serious risk of bias[4]	no serious inconsistency	serious[16]	serious[5]	none	n=66[1] median=83 days	n=66[1] median=125 days		median 42 days lower[17]	⊕⊕OO LOW	CRITICAL
Culture conversion at 24 weeks (C208 Stage 2: mITT[1]) (assessed with microbiological endpoint - MGIT960)												

1[18]	randomised trials	no serious risk of bias[4]	no serious inconsistency	serious [16]	serious[5]	none	52/66[1] (78.8%)	38/66[1] (57.6%)	RR 1.37 (1.1 to 1.77)[19]	21 more per 100 (from 6 more to 44 more)	⊕⊕OO LOW	CRITICAL
Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) [20] (assessed with: Microbiological endpoints)												
1[21]	randomised trials	Serious[22]	no serious inconsistency	serious [16]	very serious[5]	none	2/10[20] (20%)	14/27[20] (51.9%) 7/27 (25.9%)[24]	RR 0.39 (0.11 to 1.40)[23]	32 fewer per 100 (from 46 fewer to 21 more) 6 fewer (22 fewer to 34 more) [24]	⊕OOO VERY LOW	CRITICAL

[1] The mITT modified intention to treat population in C208 trial consisted of 66 subjects in each randomization group after excluding 13 subjects (16.5%) treated with bedaquiline and 15 subjects (18.5%) with placebo who did not have MDRH&R-TB or Pre-XDR-TB at baseline or for whom MGIT results were considered not evaluable.
[2] Cure defined as 5 consecutive negative cultures during final 12 months of treatment , OR, if only 1 culture is reported positive during that period, then a further 3 consecutive negative cultures from samples taken at least 30 days apart.
[3] End of study data slide supplied by Janssen subsequent to FDA meeting. In this slide, mention is made of "treatment success", but the company further clarified that the strict WHO definition of "cure" was being used
[4] Representativeness of the mITT population (assumptions made for ITT population).
[5] Small sample size and resulting large confidence interval limits precision: Few (= serious) or very few (= very serious) observations.
[6] This difference is statistically significant (Fisher p=0.005; Pearson p=0.003).
[7] Analysis on ITT population, C208 Stages 1 and 2 combined (n=102 in bedaquiline arm, 105 in placebo arm);
[8] See: Janssen, Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 (NDA 204-384), (referred to as "BD"). BD Table 2 Page 14, Table 51, Page 184; and Slide set prepared by Janssen and presented at the FDA Anti-Infective Drugs Advisory Committee Meeting, DC, 28 November 2012 (referred to as "JRD"), JRD Slide 71.
[9] Risk of side-effects (e.g. prolonged QT) could be higher if clofazimine were used; concern about follow-up being short in spite of the long half-life of BDQ.
[10] See JRD Slide 63.
[11] see BD Table 45, Appendix 4; Analysis on ITT population, C208 Stage 2 trial only (n=79 in bedaquiline arm, 81 in placebo arm); Mortality amongst all subjects exposed to BDQ in the C208 Phase 2 study, irrespective of when deaths occurred (i.e. including deaths post-120 weeks), count 10 deaths in the BDQ and 2 deaths in the Placebo group. Counting deaths strictly at the 120 weeks cut-point reveal 9 in the BDQ and 1 in the placebo group.
[12] Concern that if, in HIV patients, ARV treatment was given, there might have been drug-drug interactions affecting SAE and mortality.
[13] Fisher Exact p=0.017; Pearson p=0.014.
[14] The imbalance in deaths is unclear; clinical factors (such as HIV-status or severity of disease) and clinical outcome (disease improved or not) do not seem associated with higher/lower risk for death.
[15] see BD Figure 22.
[16] Concern re. extrapolating to general population; background treatment regimen was considered sub-optimal and not in line with WHO recommended regimens (PZA plus 4 active second-line drugs)

Appendix 3b Example of evidence to decision framework table

Question 3: Should sublingual specific immunotherapy be used for treatment of allergic rhinitis in adults without concomitant asthma?

Problem: Adults with Allergic Rhinitis

Option: sublingual specific immunotherapy

Comparison: No treatment

Setting: Outpatient

Perspective: Health Care system

Background: Background: Allergic rhinitis (AR) is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to an offending allergen. Symptoms of rhinitis include rhinorrhea, nasal obstruction or blockage, nasal itching, sneezing, and postnasal drip that are reversible spontaneously or under treatment. Allergic conjunctivitis often accompanies allergic rhinitis.

Allergic rhinitis has been traditionally subdivided into seasonal, perennial, and occupational rhinitis. Perennial allergic rhinitis is most frequently, although not necessarily, caused by indoor allergens such as house dust mites, moulds, cockroaches, and animal dander. Seasonal allergic rhinitis is most often caused by outdoor allergens such as pollens or moulds. As in a 2010 edition of ARIA guideline in this document we retained the terms “seasonal” and “perennial” to enable the interpretation of published studies, and we also include the terms used to classify AR according to the duration of symptoms as “intermittent” rhinitis (symptoms are present less than 4 days a week or for less than 4 weeks) or “persistent” (symptoms are present at least 4 days a week and for at least 4 weeks).

These guidelines do not address the issues related to diagnosis of allergic rhinitis and it is assumed that the correct diagnosis had been established before commencing treatment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	1. Overall risk of AR in adults Saudi Arabia is 90 per 1000 (79% SAR) Overall in the Middle East: • Runny nose, nasal and throat itching, postnasal drip, and nasal congestion or stuffed up nose were the most common and bothersome symptoms of AR. • 58% of participants with AR reported that the condition had an impact on their daily private and professional life. • 72% reported that limitations on their work/school activities • 35% reported that interfered with and caused them to miss work or • Sleep disturbances were shown in this survey to be extremely troubling in 15% of AR patients. (Abdulrahman H, 2012. Survey conducted in Middle East including KSA) 2. A high percentage of patients with AR surveyed missed work or had their work performance affected by allergies: work productivity decreasing by 23% in AIA, 24% in AIAP, 33% in AILA and 30% in Middle East when allergy symptoms were at their worst. Nasal allergies also interfered with many patients' sleep, and were associated with feelings of depression, anxiety, irritability and tiredness. (Blaiss 2012, America, Asia pacific, Latin America, and Middle East)	The guideline panel estimates a prevalence of 20% to 40% of AR in KSA. They consider that due to the lack of an appropiate data base with this data, the self- reporting studies could underestimate the prevalence (for not recognize the symptoms or not having a medical diagnosis) or overestimate (for considering any kind of rhinitis not only the allergic one).

Seasonal / Intermittent Allergic Rhinitis

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BENEFITS & HARMS OF THE OPTIONS	What is the overall certainty of this evidence?	No included studies ☐ Very low ☐ Low ☐ Moderate ☒ High ☐		- There is a concern that some patients in KSA would not accept SLIT with some allergen of animal origin. - Also considered that most people initially do not accept SLIT but when the symptoms not decrease with all other regular options, they accept th medication with its adverse effects. - It is considered that the lack adherence with the medicatio use is not related with its adverse effects but with the long duration of treatment.
	Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes ☐		
	Are the desirable anticipated effects large?	No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies ☐		

Outcome	Relative importance	Certainty of the evidence (SAR)
Nasal symptoms	Critical	Moderate
Ocular symptoms	Important	Low
Medication score	Important	Moderate
Symptom-medication score	Important	Moderate
Quality of life	Critical	Moderate
Serious adverse effects	Important	High
Withdrawal due to adverse effect	Critical	High
Oral pruritus or burning	Critical	High
Oral oedema	Critical	High
Gastrointestinal adverse effects	Critical	Moderate

Summary of the evidence for patients' values and preferences:

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the undesirable anticipated effects small?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	This recommendation places a relatively high value on alleviating the symptoms of rhinitis, and relatively low value on avoiding adverse effects and resource expenditure. Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable, if patients' values or preferences differ from those described here. ***Summary of findings:*** see evidence table and reference list	
	Are the desirable effects large relative to undesirable effects?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	1. SLIT was compared with standard therapy, It was (just) more effective or, in some cases, both more effective and cost-effective - SLIT is likely to be cost-effective at thresholds of £20,000; (Meadows A, 2013. SR) - These studies did not, however, report all of the utility data in a disaggregated form and all were funded by a manufacturer of SIT products (Meadows A, 2013. SR)	**- Average annual cost per patient: around 35 K SAR** **- Average cost per treatment (3 years) and patient: around 100K SAR** Average maintenance vial/ allergen/ month =707 Average 4 allergens/patient: Annual cost= 707 X 4 X 12 = 33, 936 SAR
	Is the incremental cost small relative to the net	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	benefits?			
EQUITY	What would be the impact on health inequities?	Increased ☒ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐		**Comments from the panel members:** 1. If sublingual immunotherapy use were to recommended, the health inequity will increase so t indications and the applications of SLIT should determined: The SLIT should be used only when all oth regular options do not work 2. Impact: Few patients will be affected
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐		Uncertain acceptance from patients and likely not f health care system because of cost consideration reason
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐		Implementation would require expertise and resourc (i.e. skin tests, relevant allergen) not readily available most areas.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequenc *clearly outweigh* undesirabl consequenc in most settings
	☐	☐	☒	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The KSA MoH panel suggests sublingual immunotherapy for treatment of adults with seasonal or intermittent allergic rhinitis (conditional recommendation; Moderate-quality evidence).

Appendix 4 Search strategy examples

What is the clinical disease?	Hypertension
Question or definition for the search:	Are there guidelines for hypertension?

Using a search engine like PubMed (http://www.ncbi.nlm.nih.gov/mesh), begin by searching for guidelines.

Example 1: **Searching for guidelines as a topic**

("Guidelines as Topic"[Mesh] OR "Health Planning Guidelines"[Mesh] OR "Practice Guidelines as Topic"[Mesh] OR "Guideline" [Publication Type] OR "Standard of Care"[Mesh] OR "Evidence-Based Practice"[Mesh] OR "Evidence-Based Medicine"[Mesh] OR "Clinical Protocols"[Mesh]) OR "Practice Guideline" [Publication Type]) AND "hypertension"

If the search fails to find guidelines, then the next type of search to initiate is for systematic reviews.

Example 2: **Searching for systematic reviews**

To search for systematic reviews using PubMed, take the following steps as outlined in this example:

1. Go to: http://www.ncbi.nlm.nih.gov/pubmed/clinical
2. In the search box, type in the clinical term for which systematic reviews are being sought. For example: hypertension. Click the Search button. This will generate a list of results.
3. Under the heading Systematic Reviews, look below the list of results for the words “Filter citations for systematic reviews...” and click on the hyperlink for Filter.
4. The result should then be a search strategy that allows for the retrieval of citations identified as systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, and so on.

An example of this type of search may be found below. In the event that PubMed cannot be access or another search database is being utilized, the same text below serves as an example of the type of search strategy that must be written to find systematic reviews.

(systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR

(systematic review [tiab] AND review [pt]) OR consensus development conference [pt] OR

practice guideline [pt] OR cochrane database syst rev [ta] OR acp journal club [ta] OR

health technol assess [ta] OR evid rep technol assess summ [ta])

OR

((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab])

AND

(review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR

evaluation studies[pt] OR validation studies[pt] OR guideline [pt]))

OR

((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR

(predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR

standard of care [tw] OR standards of care [tw])

AND

(survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR

handsearch [tw] OR analysis [tiab] OR critique [tiab] OR appraisal [tw] OR

(reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence)))

AND

(literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR

bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR

unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR

references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR

(clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw]))

NOT

(letter [pt] OR newspaper article [pt] OR comment [pt])

Lacking results from a guidelines or systematic reviews search, the next search would be for randomised controlled trials.

Example 3: **Searching for randomised controlled trials**

Combine the terms for the clinical condition with the search strategy below.

randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])

Appendix 5a Table format for mapping guidelines to scope questions

Availability of evidence (example form) [40]

No	Name of paper	Assessor	Scope question #1	Scope question #2	Scope question #3	Scope question #4	Scope question #5
1	Guideline 1	Name 1	No info	No info	No info	No info	No info
2	Guideline 2	Name 2	Yes pp2-4	Yes table on page 3	No info	No info	Maybe pp7-8

[40] Appraisal of Guidelines Research & Evaluation: AGREE Instrument. The Agree Collaboration, September 2001, 6-7. Available at: http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf

Appendix 5b Summary tables of recommendations of guidelines

(an example)

Guideline	Text in the guideline about the question	References	Additional information from the references if it adds anything important.	Reference for which we need to have the full text article.	Time period covered on literature search in guideline
European Society of cardiology hypertension guidelines 2007	Although the ?xed dose of the combination components limits the ?exibility of upward and downward treatment strategies, ?xed combinations reduce the number of tablets to be taken by the patient, and this has some advantage for compliance with treatment	Waeber B, Burnier M, Brunner HR. Compliance with antihypertensive therapy. Clin Exp Hypertens 1999;21:973–985. RV; Bangalore S, Kamalakkannan G, Panjrath G, Messerli FH. Fixed-dose combination improves medication compliance: a meta-analysis. J Clin Hypertens 2006;8(Suppl A):A72 (abstract). MA	Bangalore et al: A subgroup analysis of the 4 studies on hypertension showed that fixed-dose combination (pooled RR 0.76; 95% CI, 0.71-0.81; P <.0001) decreased the risk of medication non-compliance by 24% compared with free-drug combination regimen. However among the 9 studies evaluated, only 3 studies had ef?cacy outcomes. Based on these 3 studies, it can be concluded that ?xed-dose combination regimens were equally ef?cacious or, in some cases, more ef?cacious than the free-drug combination regimens.	Bangalore S, Kamalakkannan G, Panjrath G, Messerli FH. Fixed-dose combination improves medication compliance: a meta-analysis. J Clin Hypertens 2006;8(Suppl A):A72 (abstract). MA	Ends in Nov 2005
Search for newer information from Medline:	(((((("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND fixed-dose[All Fields]) AND adherence[All Fields]) NOT "review"[Publication Type]) AND "2006"[PDAT] :				
			In 2003, 87.3% of subjects were adherent to > or = 1 hypertension drug; 72.1% were adherent to their full regimen. After adjustment, we found that subjects with multidrug regimens were significantly more likely to be adherent to > or = 1 drug and significantly less likely to be adherent to their full regimen, compared with patients on a 1-drug regimen. Over one-third of subjects had elevated SBP in 2003. Both adherence measures were associated with lower odds of having elevated SBP (eg, odds ratio = 0.87 [95% CI, 0.84-0.89] for adherence to the full regimen). For subjects with multidrug regimens, partial adherence and nonadherence to the regimen were associated with higher odds of having elevated SBP.	Fung V, Huang J, Brand R, Newhouse JP, Hsu J. Hypertension treatment in a medicare population: adherence and systolic blood pressure control. Clin Ther 2007;29:972–84	

Appendix 6 Template for presenting results for a search strategy

(((((hypertension) AND fixed-dose) AND adherence) NOT "review"[Publication Type]) AND "2006"[Publication Date] : "2012"[Publication Date]) AND "0"[Publication Date] : "3000"[Publication Date]
Results: 14
1
Long-term blood pressure control: what can we do?
Neutel JM.
Postgrad Med. 2011 Jan;123(1):88-93.
PMID: 21293088 [PubMed - in process]
Related citations
2
Role of antihypertensive therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in combination with calcium channel blockers for stroke prevention.
Talbert RL.
J Am Pharm Assoc (2003). 2010 Sep-Oct;50(5):e116-25.
PMID: 20833609 [PubMed - in process]
Related citations
3
Optimizing blood pressure control in patients with chronic kidney disease.
Palmer BF, Fenves AZ.
Proc (Bayl Univ Med Cent). 2010 Jul;23(3):239-45.
PMID: 20671819 [PubMed - in process] Free PMC Article
Free full text Related citations

Appendix 7a Summary of studies table

(an example)

Guidelines

All of the guidelines recommended that hypertensive patients should limit salt intake. In seven of the guidelines (VHA, BHS, CMA, WHO, SIGN, ICSI, JNC,) specific recommendations were given regarding the maximum daily amount. While two simply recommended it be reduced (NZ, SA), eight guidelines gave practical suggestions on how this recommendation might be implemented (BHS, CMA, ISCI, WHO, SA, SIGN, JNC, ESH). Two offered no suggestions on how salt reduction might be achieved (NZ, VHA). Six guidelines (BHS, CMA, WHO, SIGN, ICSI) offered differing estimates, in the range 2-10/2.4-5 mm Hg, of the potential benefit salt reduction could have on blood pressure.

Systematic reviews

A meta-analysis of 56 was performed to evaluate the evidence on the effect of sodium restriction on lowering blood pressure in normotensive and hypertensive individuals. 28 trials included 1131 hypertensive subjects. Trials showed significant heterogeneity. Publication bias was also evident. Decreases in systolic blood pressure in response to sodium restriction of 100 mEq/day were 2.4-6.3 mm Hg in hypertensive patients. No significant effect was seen in diastolic pressure. Decreases in blood pressure were larger in trials of older hypertensive individuals.	Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. JAMA 1996;275:1590-7
A meta-analysis of seventeen trials in individuals with elevated blood pressure (n=734) was done. In individuals with elevated blood pressure the median reduction in 24-h urinary sodium excretion was 78 mmol (4.6 g/day of salt), the mean reduction in systolic blood pressure was -4.97 mmHg (95%CI:-5.76 to -4.18), and the mean reduction in diastolic blood pressure was -2.74 mmHg (95% CI:-3.22 to -2.26). The meta-analysis demonstrates a correlation between the magnitude of salt reduction and the magnitude of blood pressure reduction. Within the daily intake range of 3 to 12 g/day, the lower the salt intake achieved, the lower the blood pressure.	He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2004;(1):CD004937

References: single studies

Criteria	Patients	Interventions	Comparators	Duration	Outcome	Comments
Iles & Emerson 1974; study period: 1965-1973	32 adult patients. Diagonosis following excisional biopsy in 30 and FNA in 2.			13 episodes treated by surgery alone or with SM. The remainder treated with surgery and chemotherapy or chemotherapy alone.	In 2 patients, fresh nodes appeared during therapy.	Mean follow-up after surgery alone 10 years and relapses in 12. 5.5 year follow-up after surgery with chemotherapy and no relapses.

Appendix 7b: ROBIS instrument[41]

Phase 1: Assessing relevance (Optional)

ROBIS is designed to assess the risk of bias in reviews with questions relating to interventions, aetiology, diagnosis and prognosis. State your overview/guideline question (target question) and the question being addressed in the review being assessed:

Intervention reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Intervention(s):		
Comparator(s):		
Outcome(s):		

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Exposure(s) and comparator(s):		
Outcome(s):		

For DTA reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients):		
Index test(s):		
Reference standard:		
Target condition:		

For prognostic reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients:		
Outcome to be predicted:		
Intended use of model:		
Intended moment in time:		

Does the question addressed by the review match the target question?	YES/NO/UNCLEAR

[41] Whiting, P. *at all* ROBIS: A new tool to assess risk of bias in systematic reviews was developed. January 2016, Vol 69, Pages 225–234

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review	RISK: LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review	RISK: LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Appendix 8 Template for implementation plan

	Details	Date	Responsible institution/ person
Objective	What needs to be achieved?		
Barriers	A short description of potential barriers to implementation and how to overcome them; potential incentives.		
Key success factors	Achieving main objectives are dependent upon…? What needs to be done?		
Dissemination	A short description of channels the developer plans to use.		
Launching the guideline to stakeholders	How will the guideline be disseminated, including where, when, and to whom?		
Education and training	A short description of training needs and planned courses and seminars.		
Resources	A list of resources (on a different level) needed for implementation.		
Monitoring	A list of expected process and outcome indicators and evaluation dates, including: • Indicators description and audit targets • Standard to be achieved • Baseline assessment • Monitoring and evaluating		

Appendix 9 Template for topic proposal

		Data
Burden of disease	Mortality	
	Incidence	
	Prevalence	
	Resource impact (EHIF spending, per year)	
Variations	Practice variation	
	Health outcome variation	
	Variation in treatment costs	
Potential	Potential for updating current practice	
	Potential result on health (name measurable indicators)	
	Potential impact on resources	
Problem statement	Based on the information listed above	
Purpose of the guideline	Based on problem statement	
Guideline product	Estimated quantitative need for printed copies according to different versions of guideline product.	

Appendix 10a Template for guideline scope

Domain	Description
Title of guideline	
1. Describe the general topic	
2. Scope's content Does the potential guideline complement other programs or are there any similar guidelines available in Estonia in this particular therapeutic area? If so, will the new guideline replace or supplement the existing one(s)? Provide an overview of what the clinical guideline will include and what will not be covered: (diagnostic tests, surgery, rehabilitation, lifestyle advice).	
3. Population to be included or excluded (e.g., specific age groups or people with certain types of disease).	
4. Information and support for patients and carers to be provided.	
5. The preliminary outcomes that will be considered (benefits and potential harms to patients, impact on health insurance, society perspective).	
6. Identify the key questions (clinical, as well as organizational, regulatory, etc) following PICO format.	
7. Specialties consulted Who are the key stakeholders for implementation and for further consultation on the scope, if they have not already been involved in preparing it.	
8. Suggestions for monitoring of guideline implementation.	

Appendix 10b Rating table for outcomes

(an example)

Provisional list of outcomes for inclusion

Choose your initials from the drop down menu to the right	Initials
Do not attempt to rank the outcomes. Score each one individually from 1 – 9.	

1 – 3	Not important
4 – 6	Important, but not critical
7 – 9	Critical

Treatment	Scenario 1: Current situation – assumes no human-to-human transmission		Scenario 2: Pandemic conditions – assumes human-to-human transmission is present	
Outcome	Initials	Relative importance	Initials	Relative importance
Mortality rates Duration of hospitalisation LRTI Duration of disease Drug resistance Serious adverse effects Cost of drugs Other costs / potential savings Viral shedding Outbreak control Withdrawals due to adverse effects / mild adverse effects Hospitalisation				

Prophylaxis	Scenario 1: Current situation – assumes no human-to-human transmission		Scenario 2: Pandemic conditions – assumes human-to-human transmission is present	
Outcome	Initials	Relative importance	Initials	Relative importance
Influenza cases Influenza cases (asympt) Mortality rates Duration of hospitalisation Duration of disease Viral shedding Outbreak control Drug resistance Serious adverse effects Withdrawals due to adverse effects Cost of drugs Potential savings				

Appendix 11 Algoritm of the Clinical Pathway, an example