



ESTONIAN HANDBOOK FOR GUIDELINES DEVELOPMENT

2011

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Acronyms and Terms

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

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| AMSTAR | Assessment of Multiple 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. There was an agreed guideline development handbook for the health-care sector developed by the Estonian Health Insurance Fund (EHIF), which is also accepted by the Estonian medical societies. Since 2003, numerous guidelines, protocols and clinical pathways were developed by various organizations within the health system. However, as there was no uniformly accepted single Estonian national approach to guideline development, this resulted in a wide array of guideline formats.

In 2010, a comprehensive assessment of the situation was made by the World Health Organization (WHO), EHIF, the Medical Faculty at the University of Tartu, and national and international experts in an effort to streamline and harmonize the principles and processes of guideline development in Estonia from 2011 onwards.

An updated process, described in a new 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 process has been developed in consultation with WHO experts and has been tested in Estonia through a pilot project consisting of development of a new guideline during 2010-2011 on the management of hypertension in primary care.

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.

1 Introduction

1.1 Guidelines definition

A guideline is a document that contains recommendations about health interventions. It provides guidance for health-care providers about evidence-based options for diagnosis and care of patients. This may include prevention, pharmaceutical treatment, surgical techniques, patient education strategies, and other types of choices. It provides the information that guides choices between different interventions that may have an impact on health and that have an influence on resource use.

The need for country-specific guidelines is envisaged in most clinical specialities. 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 (see [Chapter 3: Topic proposal and selection](#)).

1.2 Overview of the guideline development process

The process for guideline development has to be fully transparent, carefully con-

sidered, and created in close cooperation with all stakeholders. The process does not end with approval of the guideline; further action is needed to ensure that the guideline is implemented not only in practice, but that its stated objectives are achieved.

A need for a guideline can be identified by any organization (i.e. professional society, patient group, academic institution, etc). The guideline initiator should submit a topic proposal (see [Chapter 3: Topic proposal and selection](#)) and a draft scope (see [Chapter 4: 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 (see [Chapter 2: Guideline development groups](#)).

Development of a guideline is overseen by a multidisciplinary Guidelines Panel in close collaboration with the Guidelines Secretariat (see [Chapter 2](#)). 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 Medical Faculty at the University of Tartu and the EHIF.

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 guideline 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.

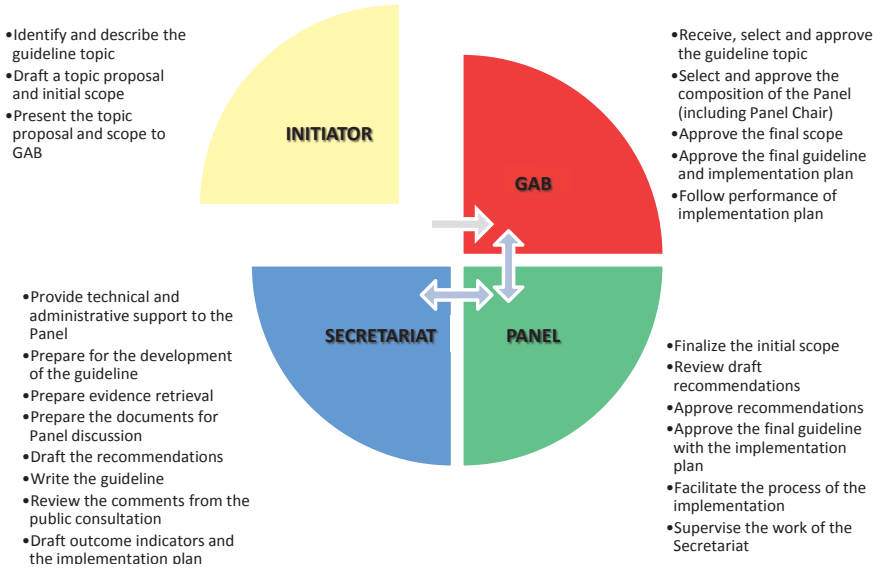
1.3 The guideline development process



2 Guideline development groups

2.1 Groups

2



2.2 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 other 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.

2.2.1 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 (hereafter “Panel”) and nominate the Chair of the Panel;
- Approve the draft scope presented by the Panel;
- Evaluate declarations of interest (DOI) 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.

2.2.2 Composition of the GAB

GAB should include members nominated by the following institutions:

Faculty of Medicine, University of Tartu
Estonian Medical Association
Estonian Society of Family Physicians
Estonian Nurses Association
Estonian Hospital Association
Estonian Chamber of Disabled People
Institute of Public Health, University of Tartu
National Institute for Health Development (NIHD)
Estonian Health Insurance Fund (EHIF)

Ministry of Social Affairs (MoSA)
State Agency of Medicines (SAM)
Health Care Colleges

All members of the GAB are required to complete declaration of interest forms before the process of topic selection is undertaken each year (see [Chapter 3](#)).

Members of the GAB should meet as needed but at least twice a year: In March, to consider and approve topics; and in October, to review progress, provide guidance, if necessary, and approve the final guideline for implementation. If additional time is needed, the Panel may continue its work to the following March.

2.3 The Guidelines Panel

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

2.3.1 Tasks of the Panel

- 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.
- Review draft recommendations based on the presented evidence, 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.
- Approve recommendations, taking into account values and preferences, according to GRADE, and cost implications.
- 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.

2.3.2 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 guidelines panel should be small enough for effective group interaction, but large enough to ensure adequate representation of relevant views.

2.3.3 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.

2.3.4 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.

2.3.5 Panel meetings

To be effective, the Panel will need to convene at least 2-3 face-to-face meetings. The purpose of the first meeting is to develop the clinical questions so that the scope of the proposed guideline may be finalized. At the second meeting, the Panel should review recommendations based on evidence prepared by the Secretariat. A final meeting might include approving the final guideline, indicators for assessment of implementation of the guideline, 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.

If the purpose of the meeting is to formulate recommendations:

- distribute the evidence profiles prepared by the Secretariat before the meeting. (GradePRO software is available and may be used

- without cost);
- 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.

2.4 Secretariat

2.4.1 Tasks of the Secretariat

- Prepare for the development and writing of the guideline, according to the Panel's guidance.
- Provide technical support for developing the guideline, including preparation of documents that will aid the Panel in their decision-making; evidence retrieval for recommendations; 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, including organizing the 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.

2.4.2 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.

2.4.3 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 assistant:** provides administrative support, arrangement of the meetings, etc.

2.4.4 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 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 may include:

- discussion of the guideline scope in order to form a basic strategy for a literature search;
- primary screening of retrieved guidelines in order to select papers for assessment using the AGREE instrument;¹
- clarification of discrepancies between assessments² and mapping the availability of evidence for each question (see [Appendix 4c](#));
- creation of a web-based search strategy for primary references (i.e. reports of clinical trials, meta-analyses, etc.) for questions for which there is no available material from guidelines. Search strategies and their re-

¹ Appraisal of Guidelines Research and Evaluation Instrument.

See <http://www.agreecollaboration.org/instrument/>.

² Each guideline should be assessed by at least two assessors. See Section 5.5.2

- sults must be clearly documented (see [Appendix 4b](#));
- appraisal of the primary references with the help of the GRADE instrument;
 - 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 guideline³ (See [Appendix 4f](#));
 - suggesting a process and/or outcome indicators for monitoring of the implementation of the guideline;
 - preparation of an implementation plan.

³ The summary should be sent to the Panel Chair at least two weeks prior to the relevant meeting.

3 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.

See http://www.who.int/ipcs/methods/harmonization/areas/mutagenicity_doi.pdf.

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 member should complete and submit a declaration of interests (DOI) (see [Appendix 1: Declaration of Interests](#)) to the GAB. The GAB will then decide whether the declaration contains any conflicts that should result in the exclusion of a proposed Panel member.
- Once the Guideline Panel is approved by the GAB, the administrative assistant should collect these 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 should verbally report potential conflicts of interest. Any con-

flicts of interest that are identified should be managed according to the rules agreed to by the GAB. 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 a Panel member's DOI should be recorded in the minutes of the meeting. If a panelist has a conflict of interest, the panelist has the same options as those outlined for nominees. The exception is the third option, wherein the panelist may be asked to submit their resignation from the Panel.

- Additionally, all Secretariat members are required to complete and submit DOIs. The same rules about DOIs and COIs apply to Secretariat members as apply to the Chair and the panelist.
- DOIs will be published in the final, full guideline.

4 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’.

4

4.1 Selecting and 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. (It should be noted that it is not appropriate for pharmaceutical manufacturers to initiate topics, as this may present major conflicts of interest.) The individual or organization proposing the topic is subsequently called “the initiator”. (See [Appendix 2](#) and [Appendix 3a](#).)
- Topics, together with their initial scope, must be presented by the initiator to the GAB once a year, no later than 1 February (see [Appendix 2](#) and [Appendix 3a](#)).
- Topics 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 proposals must include statistical data. Acquiring this data will require active communication between the initiator and potential stakeholders, including EHIF.

4.2 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) (see [Chapter 4: The scope of the guideline](#)). 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.

4.3 How are topic(s) selected?

Based upon the criteria listed below, the GAB will assess the topics using the draft scope documents presented to them by 1 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).

4

The GAB will evaluate topics based on their assessment of:

- **Problem statement and the purpose of the guideline**
 - The **problem statement** is drafted by the initiator based on the information listed above. 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.)⁴
 - service treatment (all treatment costs within a certain period)
 - pharmaceuticals

⁴ Treatment cost analyses can be conducted using data from the EHIF database, which may be obtained on request.

- hospitalization (rate, length of stay, etc.)
- **Potential**
 - **potential for modernization** of current practice
 - availability of new interventions (including diagnostic tests and strategies)
 - 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 3a: Template for scope](#))
- **Relationship of topics and scope to health related government priorities**

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 proposal⁶

5 The scope of the guideline

5.1 What is the scope?

The scope provides a framework within which to conduct the guideline development work.

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

5

5.2 Who prepares the scope?

The initial scope, with questions and perceived outcomes, 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.

5.3 Drafting the initial scope

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);
- health-care settings (primary or specialized care);
- the different types of interventions and treatments to be included or excluded (diagnostic tests, surgery, rehabilitation, lifestyle advice). Does the potential guideline complement other programs or interventions in the particular therapeutic area?
- information and support for patients and their care-givers and health care providers;
- the outcomes that will be considered (benefits and potential harms to patients, impact on health insurance, societal perspective);
- 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 and what will not be covered;
- identifies the key questions (clinical, as well as organizational, regulatory, etc). It is useful to formulate the questions using the PICO format (see Section 4.4: Formulating questions for the scope);
- chooses and rates the outcomes (see Section 4.5: Choosing and rating 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 30 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 3a](#).

5.4 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 questions are also 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.

It is helpful to start by dividing the types of information and 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 effectiveness of an HPV vaccine?

What types of surgical interventions are used for low back pain?

Recommendation/decision

Should we use HPV vaccine?

Should patients with low back pain be offered surgery?

Guidelines may include all three categories.

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 facts/foreground questions are the most important ones for a guideline. They are used to inform the recommendation/decision and the quality assessment of the evidence using the GRADE approach.

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.

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 is the frequency of the problem? (background)
- What causes the problem? (etiology)
- 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 5.1: PICO framework

| Factor | Descriptor/Question | Example |
|------------------------------------|--|--|
| Population | What factors are essential? | <i>In adults (>18 years of age) and the elderly (over 75 years of age) with confirmed hypertension...</i> |
| Indicator/ Intervention | Specific intervention or class? | <i>...does dietary advice concerning salt restriction...</i> |
| Comparator | Compared with doing nothing or with standard treatment | <i>...compared with no salt restriction...</i> |
| Outcome | Patient-relevant outcomes, including both benefits and potential side effects and over what period of time (e.g. mortality at two years) | <i>...lower blood pressure and/or reduce mortality?</i> |

This format can also be used, with slight modifications, for questions on prevalence and incidence, etiology (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, C) accurately detect disease?*

5.5 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).

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

Step 2. 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.

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 or other open source solution (e.g. online survey applications, which allow the user to prepare an interactive survey and send a link to participants.)

5.6 Identifying resource implications

Once the key questions are formulated, the initiator should list 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. Further aspects of the evaluation of cost and resource use for recommendation development are in Section 7.

5.7 Finalising the scope

Topics, together with their initial scope, must be presented to GAB according to the templates for scope and implementation (see Appendix 3a and Appendix

5) by or on 1 February. The GAB will assess the topics together with the initial scope documents and will or will not approve topics for guideline development. The GAB will consult and approve the composition of the Guidelines Panel.

The Panel may revise the initial scope based on the clinical 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.**

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The final scope will be presented by the Panel and approved by the GAB.

6 Evidence retrieval

6.1 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 in [Section 5.3: 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 from a hierarchy of sources, including:

1. recommendations developed from published clinical guidelines that were created by independent national authorities (e.g., NICE) and that meet specified criteria (see [Section 5.2: Prioritizing evidence retrieval](#));
2. recommendations developed from published clinical guidelines that were created by non-commercially funded specialty societies, and that follow standardized criteria for guidelines;
3. recommendations developed from published clinical guidelines that were created by commercially funded specialty societies, that provide

evidence summaries and adequate descriptions of the processes used to manage conflicts of interest;

4. recommendations developed from existing systematic reviews.

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

Systematic reviews that are used will also be assessed for quality using the latest version of the AMSTAR checklist.

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.

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6.2 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 (see [Section 4: The scope of the guideline](#)).

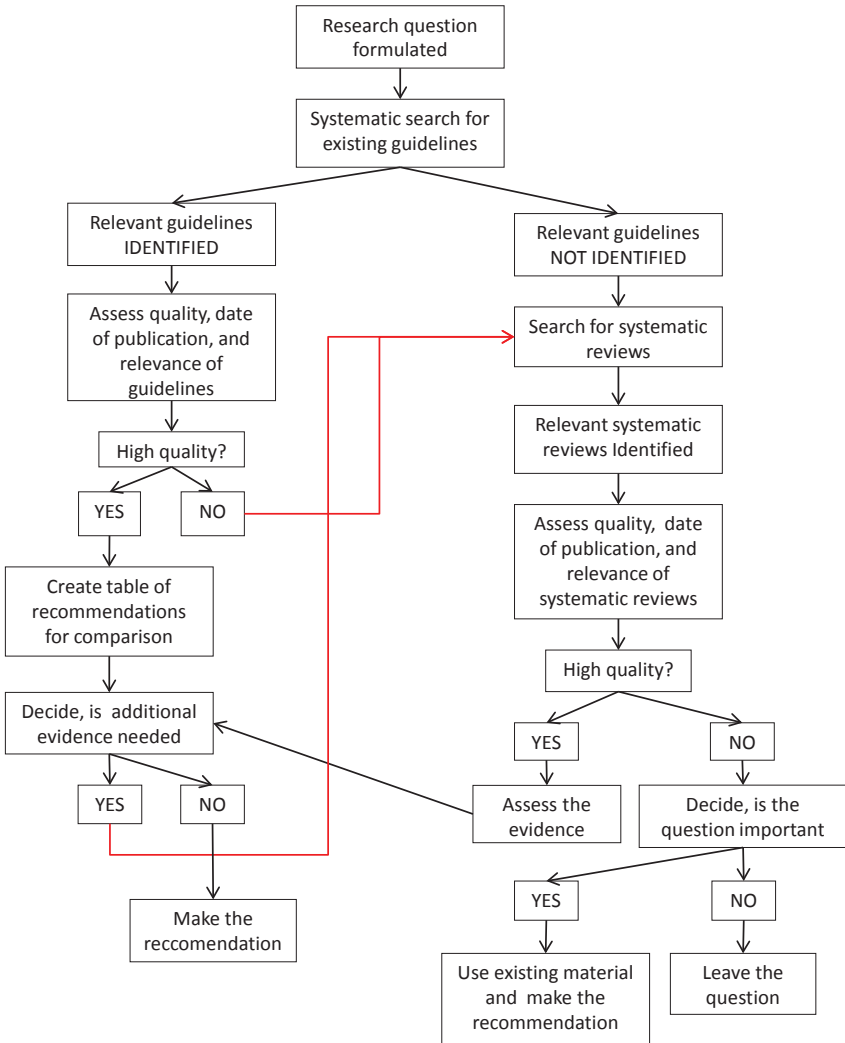
To avoid performing a duplicate search or creating a duplicate guideline, the process outlined below starts by 1) using existing guideline recommendations, and checking the evidence for them, then 2) describes the full process of developing recommendations based on systematic reviews, and 3) includes 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.⁵

6.3 The process of evidence retrieval

The process of evidence retrieval, assessment, and synthesis is described in further detail below and is summarized in the figure below.

⁵ The Cochrane Handbook for Systematic Reviews of Interventions is available at: <http://www.cochrane.org/training/cochrane-handbook>.

Figure 6.1: Evidence retrieval, assessment, and synthesis process



6.4 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)⁶
- websites of guideline-producing agencies:
 - 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>
 - Finnish Current Care: <http://www.kaypahoito.fi/web/english/home>
- 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 4a and Appendix 4b. 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.

⁶ 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 tables, summary of findings tables, 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 4c.

2) what is the quality of the guideline, based on the AGREE rating instrument?

The key questions in the AGREE instrument relevant to quality of a guideline for subsequent consideration are 8-11 and 22-23 (see Text box 5.1). Ideally two members of the Secretariat should assess each guideline and the individual ratings should be compared. If these six questions score a total of 12 or less by each rater, the guideline is probably too poor in quality to be useful.

Text box 6.1: AGREE instrument questions 7-11 and 22-23⁷

Q7: Systematic methods were used to search for evidence.
(4 Strongly Agree ... 1 Strongly Disagree)

Q8: The criteria for selecting the evidence are clearly described.
(4 Strongly Agree ... 1 Strongly Disagree)

Q9: The strengths and limitations of the body of evidence are clearly described.
(4 Strongly Agree ... 1 Strongly Disagree)

Q10: The methods used for formulating the recommendations are clearly described.
(4 Strongly Agree ... 1 Strongly Disagree)

Q11: The health benefits, side effects and risks have been considered in formulating the recommendations.
(4 Strongly Agree ... 1 Strongly Disagree)

Q22: The views of the funding body have not influenced the content of the guideline.
(4 Strongly Agree ... 1 Strongly Disagree)

Q23: Competing interests of guideline development group members have been recorded and addressed.
(4 Strongly Agree ... 1 Strongly Disagree)

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,

⁷ Appraisal of Guidelines Research & Evaluation II: AGREE II Instrument. The Agree Collaboration, September 2009, 6-7. Available at: <http://www.agreetrust.org/?o=1397>.

values and preferences, and feasibility (see [Section 8: 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 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.

6.5 Retrieving existing systematic reviews

6.5.1 Why use 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 (see below See [Section 5.5.2: Finding systematic reviews](#)). 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).

6.5.2 Finding systematic reviews

The first step is to identify relevant systematic reviews for each of the questions⁸, 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.

6.5.3 Assessing the quality 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;⁹
- 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);
- quality, which may be assessed by using the AMSTAR instrument, a standard critical appraisal instrument (see Text box 6.2 below). Ideally, this should be done by two members of the Secretariat.

Based on the AMSTAR instrument, reviews may be excluded from further use if both raters agree that there were no prespecified criteria for including studies (Question 1) and there are concerns about the conflict of interest declaration

⁸ For information on search strategy, see Sections 5.3 and 5.4.

⁹ Even then, they should be used with great care as the risk of selection bias for including studies or outcomes is very high!

¹⁰ Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007 Feb 15;7:10

(question 11). 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.

Text box 6.2: AMSTAR instrument¹⁰

| | |
|---|---|
| <p>1. Was an ‘a priori’ design provided? The research question and inclusion criteria should be established before the conduct of the review.</p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p> |
| <p>2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.</p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p> |
| <p>3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.</p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p> |
| <p>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.</p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can’t answer <input type="checkbox"/> Not applicable</p> |

| | |
|---|---|
| <p>5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |
| <p>6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |
| <p>7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |
| <p>8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |
| <p>9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |

| | |
|--|---|
| <p>10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |
| <p>11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't answer <input type="checkbox"/> Not applicable |

6.6 Presentation of recommendations and results to the Panel

The Secretariat needs to prepare summary tables that include 1) the recommendations from included guidelines and 2) results relevant to each question and outcome from guidelines and systematic reviews to present to the Panel.

For summary tables of recommendations of guidelines, the table template is in [Appendix 4f](#).

For summary tables of results from systematic reviews for each question and its outcomes, GRADE evidence profiles may be used (see below), or study-by-study tables, using the template in [Appendix 4e](#).

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 summarises the general presentation of results in systematic reviews.

7. Grading the quality of evidence

Assessing the evidence retrieved is a crucial step that enables the guideline panel to formulate recommendations. The GRADE system for preparing evidence profiles, assessing quality of evidence and developing recommendations should be used to summarise systematic reviews if there are no evidence profiles in existing guidelines, and to present evidence to the Panel. This is particularly important when there are discrepancies in recommendations across guidelines, which need to be resolved.¹¹ 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.

7

If there are no GRADE evidence summaries, the Guideline Panel will have to decide whether to retrieve the systematic reviews on which the recommendations are based, and prepare evidence summaries, or simply use the existing recommendations, and apply considerations of cost, local values and preferences, and feasibility. For potentially high-cost interventions, it is strongly suggested that the systematic review be retrieved and evidence summaries prepared.

The GRADE profiler includes all the instructions for developing GRADE evidence profiles and for assessing the quality of evidence and developing recommendations. Free software may be downloaded from:

<http://www.flintbox.com/public/project/1537>

or <http://www.gradeworkinggroup.org/toolbox/index.htm>.

A brief overview of the GRADE approach is provided below. For further information, please use the GRADE Working Group website.

7.1 Using GRADE

The GRADE approach has two main steps: evaluation of the quality of evidence and preparation of a summary of findings.

7.1.1. Evaluation of the quality of evidence

Quality 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

¹¹ To access GRADE, go to <http://www.gradeworkinggroup.org>.

involves some degree of arbitrariness. It is based on the following criteria:

- study design and any limitations of the studies, in terms of their conduct and analysis;
- the consistency of the results across the available studies;
- the precision of the results (wide or narrow confidence intervals);
- the directness (or applicability 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 7.1: Quality of evidence and their definitions

| Grade | Definition |
|--------------|--|
| High | Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very low | Any estimate of effect is very uncertain . |

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

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

Table 7.2: A summary of GRADE’s approach to rating quality of evidence¹²

| Study design | Initial quality of a body of evidence | Lower if | Higher if | Quality of a body of evidence |
|-----------------------|---------------------------------------|---|--|--|
| Randomised trials | High ⇒ | Risk of Bias - 1 Serious - 2 Very serious | Large effect + 1 Large +2 Very large | High (four plus: ⊕⊕⊕⊕) |
| | | Inconsistency - 1 Serious - 2 Very serious | Dose response +1 Evidence of a gradient | Moderate (three plus: ⊕⊕⊕O) |
| Observational studies | Low ⇒ | Indirectness - 1 Serious - 2 Very serious | All plausible residual confounding +1 Would reduce a demonstrated effect | Low (two plus: ⊕⊕OO) |
| | | Imprecision - 1 Serious - 2 Very serious | Publication bias - 1 Likely - 2 Very likely | Very low (one plus: ⊕OOO) |

7

7.1.2. 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.

GRADE tables are 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. For each outcome, data should be presented from the subset of studies in the review that reported it.

Fill in the column, 'number of studies'. This is the number of studies in the review that

¹² GRADE Working Group, <http://www.gradeworkinggroup.org>.

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. 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 evidence profiles 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.

7.2 Presenting the evidence to the Panel

Draft evidence summaries, and tables, including GRADE profiles, and a draft assessment of costs, values and preferences, and feasibility, 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 summaries. The final summaries are then used as the basis for drafting recommendations. A template for presenting this information is in [Appendix 4f](#).

8 Assessing cost 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.¹³ This evaluation should be coordinated with the guideline development process, if possible, to avoid duplication of processes. A parallel process is coordinated by EHIF.

8.1 Budget impact assessment

8

The Guideline 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. 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?*)

¹³ 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/834210?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/119112010004?leiaKehtiv>.

- 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.

8.2 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 devel-

oping 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.

8

8.3 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 (see [Section 8: Developing recommendations, for a definition](#)) 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.

9 Developing recommendations

9.1 Draft recommendations

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

See Chapter 2: Guideline development bodies, for further information on the Guideline Panel. A Guideline Panel may need to hold several meetings over the course of 12 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 4f](#).

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). 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).

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

9.2 How does the panel decide on recommendations?

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 Section 2.3.5.)

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

- the draft recommendations are presented by the Secretariat, with a justification and reference to the relevant evidence (evaluated by GRADE) summary;
- 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;
- if necessary, the first recommendation is modified;
- final agreement on the recommendation is reached.

9.3 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 (see Table 8.1). The Guideline Panel should consider all these factors and make the reasons for their judgments explicit.

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 9.1: Factors that may influence the strength of recommendations¹⁴

| 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 |
| 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. To ensure that end users will un-

¹⁴ 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

derstand 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 below.

Table 9.2: 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 |

9.4 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 proc-

esses 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.

10 Implementation

10.1 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
- 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.

10.2 Guideline implementation

Successful implementation of the guideline depends on the effectiveness of the implementation process and its awareness and acceptance of it 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.

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.
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.
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.
8. **Define feedback** and reporting of implementation to the GAB after a predefined time period.
9. **Determine clear roles and responsibilities** for each action.
10. **Determine milestones with timescales** for each stage of the implementation process.

A template for the Implementation Plan is in [Appendix 6](#).

11 Updating a guideline

The prepared guideline should generally be updated five years after publication. Updating should be considered earlier, 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.

12. 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.¹⁵

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

¹⁵ Grol R, Wensing M, and Eccles M, *Improving Patient Care: The Implementation of Change in Clinical Practice*. Elsevier Butterworth Heinemann, Edinburgh, 2005, 283.

do not. They often rely on medical records and patient recall for data collection. These types of studies are less reliable than randomized controlled trials and cohort studies, because showing a statistical relationship does not mean that 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 4, Table 4.1: 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.¹⁶

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.¹⁷

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.¹⁸

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).¹⁹

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.

Dichotomous outcomes: Any outcome measure in which there are two possibilities such as dead/alive, admitted/discharged, pregnant/not pregnant, and where

¹⁶ 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.

¹⁷ *Ibid*

¹⁸ *Ibid*

¹⁹ *Ibid*

the patient must be in one, but cannot be in both categories.²⁰

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.²¹

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 financier 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>.

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.

²⁰ 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.

²¹ *Ibid* 411

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 9.2: Guideline implementation and Appendix 5: 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.²²

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, 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>

²² Incremental cost effectiveness ration, Health Economics Glossary of Terms. At: http://www.healtheconomics.nl/W/Incremental_cost_effectiveness_ratio

²³ 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.

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.²³

Peer review: A process of subjecting scholarly works, research, or ideas to the scrutiny of others who are experts in the same field.²⁴

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 4, Table 4.1: 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.²⁵

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.

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.

²⁴ 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>.

²⁵ 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.

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

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Appendix 1 Declaration of interests form (Example)

Note: The example provided below is the Declaration of Interests form used by the World Health Organization.

DECLARATION OF INTERESTS FOR WHO EXPERTS

The assistance of distinguished authorities knowledgeable in a variety of medical and scientific professions is essential to the solution of international health issues. It is expected that persons qualified to serve as an expert for the World Health Organization (WHO) may have private interests related to the subject of their expertise. At the same time, it is imperative that situations be avoided in which such interests may unduly affect, or may be perceived to affect, an expert's impartiality or the outcome of work in which he/she was involved.

To assure the highest integrity, and hence public confidence, in the activities of Organization, WHO regulations and policies require that all experts serving in an advisory role disclose any circumstances which could give rise to a potential **conflict of interest** (i.e., any interest which may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). Accordingly, in this Declaration of Interest form, you are requested to disclose any financial, professional or other interest relevant to the subject of the work or meeting in which you will be involved and any interest that could be significantly affected by the outcome of the meeting or work. You are also asked to declare relevant interests of others who may, or may be perceived to, unduly influence your judgment, such as immediate family members, employers, close professional associates or any others with whom you have a substantial common personal, financial or professional interest.

Kindly complete this form and submit it to the WHO Secretariat, well in advance of the meeting or work. You are also asked to inform the Secretariat of any change in this information that occurs before or during the course of the meeting or work. If WHO considers that a potential conflict of interest exists, one of several outcomes can occur, depending on the circumstances involved: (i) you may be invited to continue to participate in the meeting or work, provided that your interest would be publicly disclosed; (ii) you may be asked not to take part in the portion of the meeting, discussion or work related to your interest, or not participate in related decisions; or (iii) you may be asked not to take part in the meeting or work altogether. Non-completion of

the DOI form would preclude further consideration of an expert's participation.

Experts are requested to agree that any relevant conflicts may be **publicly disclosed** to other meeting participants and in the resulting report or other work product. The Secretariat will assume that you consent to such a disclosure, unless you check "no" in the space provided on the last page of this form. The information disclosed by you **may later be made available** to persons outside of WHO if the objectivity of the work or meeting in which you are involved is questioned and the Director-General considers disclosure to be in the best interests of the Organization, although only after discussion with you.

Name:

Institution:

Email:

Date and title of meeting or work, including description of subject-matter to be considered (if a number of substances or processes are to be evaluated, a list should be attached):

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself, your employer and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your minor children). "Commercial entity" includes -- aside from any commercial business -- an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources having an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past 3 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work? Please also report any application or negotiation for future work.

1a Employment

Yes No

1b Consulting, including service as a technical or other advisor

Yes No

RESEARCH SUPPORT

Within the past 3 years, have you or your department or research unit received support or funding from a commercial entity or other organization with an interest related to the subject of the meeting or work? Please also report any application or award for future research support.

2a Research support, including grants, collaborations, sponsorships, and other funding

Yes No

2b Non-monetary support valued at more than US\$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)

Yes No

INVESTMENT INTERESTS

Do you have current investments (valued at more than US\$10 000 overall) in a commercial entity with an interest related to the subject of the meeting or work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified.

3a Stocks, bonds, stock options, other securities (e.g., short sales)

Yes No

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures)

Yes No

INTELLECTUAL PROPERTY

Do you have any current intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (also include pending applications)

Yes No

4b Proprietary know-how in a substance, technology or process

Yes No

PUBLIC STATEMENTS AND POSITIONS

(during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization?

Yes No

5b Have you held an office or other position, paid or unpaid, where you may be expected to represent interests or defend a position related to the subject of the meeting or work?

Yes No

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product which is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a financial or commercial competitive advantage?

Yes No

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, financial or professional interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?

Yes No

6c Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?

Yes No

TOBACCO OR TOBACCO PRODUCTS

(answer without regard to relevancy to the subject of the meeting or work)

7 Within the past 3 years, have you had employment or received research support or other funding from the tobacco industry or had any other professional relationship with an entity, directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?

Yes No

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is "yes", check above and briefly describe the circumstances on this page. If you do not provide, the amount or value of the interest, where requested, it will be assumed to be significant.

| Nos. 1 – 4, 7: Type of interest, question number and category (e.g., Intellectual Property 4.a copyrights) <u>and</u> basic descriptive details. | Name of company, organization, or institution | Belongs to you, a family member, employer, research unit or other? | Amount of income or value of interest (if not disclosed, is assumed to be significant) | Current interest (or year ceased) |
|--|---|--|--|-----------------------------------|
| | | | | |
| Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant detail | | | | |

CONSENT TO DISCLOSURE. The Secretariat will assume that you consent to the disclosure of any

relevant conflicts to other meeting participants and in the resulting report or work product, unless you check "no" in the space provided here. If you check "no", the Secretariat will not disclose the information without your prior approval, although this may result in your not being able to participate in the meeting or conference. No:

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information due to the fact that I acquire additional interests, I will notify the responsible staff of WHO and complete a new declaration of interests detailing the changes. This includes any change which occurs before or during the meeting or work itself and through the period up to the publication of the final results.

Date: _____ Signature _____

Appendix 2 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 impact on health (name measurable indicators) | |
| | Potential impact on resources (name measurable indicators) | |
| 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 3a Template for guideline scope

| | |
|---|---|
| 1. Title of guideline | |
| 2. Content issue | |
| 2.1 Population | <p>The population/target group to be covered/excluded by the guideline (for examples specific age group or people who have certain illness)</p> <p>Example: Adults (>18-years) with essential hypertension, including patients with pre-existing cardiovascular disease and/or diabetes (type II or I) elderly people (defined as over 75 years). Excluded children <18 and pregnant woman.</p> |
| 2.2 Health-care setting or level of health care?? | <p>Level of health care (primary or second level) where will implement this guideline</p> <p>Will implement in primary care level</p> |
| 2.3 key questions that will be covered together | <p>Each question with outcomes</p> <p>Example:</p> <ul style="list-style-type: none"> - Should all adult patients with suspected hypertension be investigated with 24 hour ambulatory blood pressure monitoring compared to standard blood pressure measures? - Should all patients with confirmed hypertension be offered dietary advice concerning salt restriction, compared with no salt restriction? |
| 2.4 key questions that will not be covered | <p>Example:</p> <p>Screening and prevention of hypertension in adult population (should be covered by another national guideline (on cardiovascular prevention)</p> <p>Smoking cessation strategies (covered by another national guideline, but <u>note that final guideline will have recommendation about advice to stop smoking</u>);</p> <ul style="list-style-type: none"> - Exact diagnosis and management of secondary hypertension; - Hypertension during pregnancy (covered by another national guideline) - Diagnosis and management of children and adolescents with hypertension (need for a separate guideline to be assessed); - Management of dyslipidaemia and weight problems (covered by another national guideline, <u>reference to be included in the final guideline</u>); - Management of hypertensive crisis, hypertensive emergencies; - Management of patients with hypertension with end stage renal disease. |

| | |
|---|--|
| <p>2.5 key resource issues that should be considered</p> | <p>Different resources needs during the implementing of guideline (Money, human capital or workforce?, equipments etc) Example: Cost-utility/cost-minimisation analyses to be carried out when making recommendations involving a choice between alternative interventions which may cause a budget impact of measurable size</p> |
| <p>3. Specialties consulted</p> | <p>Cardiology, nephrology, nursing</p> |
| <p>4. Suggestions for monitoring of guideline implementation.</p> | <p>Possible indicators with expecting outcomes Examples:</p> <ul style="list-style-type: none"> - Expected increase in proportion of adults with hypertension treated by family physicians compared to cardiologists/other specialist; - Decrease in amount of variations (diagnostics, treatment) in primary care hypertension treatment; - Increase in number of consultations (non-pharmacological interventions) performed by family nurses; - Better BP control rates; |

Appendix 3b Rating table for outcomes (Example)

Outcomes are identified during scoping-a few examples are given below. Each member of the guideline panel should then rate them according to importance using a 1-9 scale (1-3 not important, 4-6 important, but not critical, 7-9 critical)

| Possible outcomes | Score in the scale 1-9 |
|---------------------------------|------------------------|
| Hospitalisation | |
| Duration of disease | |
| Duration of hospitalisation | |
| Drug resistance | |
| Cost of drugs | |
| Serious adverse effects | |
| Other costs / potential savings | |
| Mortality | |

Appendix 4a Search strategy (Example)

| | |
|---|--|
| 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 treb* [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 4b Presenting results for a search strategy (Example)

((((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, Fennes 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 4c Table format for mapping guidelines to scope questions ²⁶ (Example)

Availability of evidence

| 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 |

²⁶ Appraisal of Guidelines Research & Evaluation: AGREE Instrument. The Agree Collaboration, September 2001, 6-7. Available at: <http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf>

Appendix 4d Summary tables of recommendations of guidelines (Example)

| Guideline | Text in the guideline about the question | References | Additional information from the reference 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 ?xibility 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, Panjirath G, Messerli FH. Fixed-dose combination improves medication compliance: a metaanalysis. 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 efficacy outcomes. Based on these 3 studies, it can be concluded that ?xed-dose combination regimens were equally effective as compared with free-drug regimens. The free-drug combination regimens. | Bangalore S, Kamalakkannan G, Panjirath 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"[PPDAT]) | | | | |
| | | | 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 multiring 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 multiring 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 4e Summary of studies table (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

| | |
|---|--|
| <p>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.</p> | <p>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</p> |
| <p>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.</p> | <p>He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2004;(1):CD004937</p> |

References: single studies

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

Appendix 4f Evidence to recommendation table (Example)²⁷

| Recommendation: In patient with HIV and drug resistant TB requiring second line drugs, the expert panel recommend/suggest to (not) administer ART (? Recommendation, ? quality evidence) | | | |
|--|-----------------------|--|---|
| Population: HIV positive individuals with drug resistant TB requiring second line drugs | | | |
| Intervention: ART use during TB treatment v AT non-use | | | |
| Factor | Decision | Explanation | |
| High or moderate quality evidence (is there high quality evidence?) The higher the quality of evidence, the more likely is a strong recommendation. | Yes No | $\oplus \oplus \bigcirc \bigcirc$ | There is limited evidence from published studies to evaluate ART use in HIV-TB coinfecting patient's receiving second line drugs for XDR-TB and MDR-TB. However, using IPD from longitudinal cohort studies, we found moderate quality evidence from observational studies that there |
| Certainty about the balance of benefits versus harms and burdens (is there certainty?) The larger the difference between the desirable and undesirable consequences and certainty around the difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/week recommendation. | Yes No | Although there is some uncertainty about cure, there is a significant decrease in hazards ratio for death even after controlling for initial CD4 count | <ul style="list-style-type: none"> • Cure and survival appear to more likely in drug resistant TB requiring second line drugs if ART is used during TB treatment. <ul style="list-style-type: none"> ○ HR of 3.17 (1.46, 6.9) for cure and HR of 0.41 (0.26, 0.63) for death in ART vs. Non ART group. ○ No significant change in HR for cure (HR 2.93 (0.98,8.69)), and decreased HR for death (HR 0.23 (0.12, 0.46)) if controlling for initial CD4 count (HR 0.23) |
| Certainty or similarity in values (is there certainty?) The smaller variability or uncertainty around values and preferences, the more likely is a conditional or week recommendation. | Yes No | | <ul style="list-style-type: none"> • Little regarding the outcomes of cure and survival. Significant uncertainty regarding effects of ART on other outcomes, including adverse elements, default, time to smear and culture conversion and timing of ART initiation. |
| Resource implications (are the resources consumed worth the expected benefit?) The higher the costs of an intervention compared to the alternative that is considered and other cost related to the decision – that is, the more resources conditional/week recommendation. | Yes No | More resources required for concomitant ART use | <ul style="list-style-type: none"> • Need for more skilled providers trained in HIV and drug resistant TB care and drug-drug interactions. |
| Overall strength of recommendation | Strong or conditional | | |

²⁷ 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

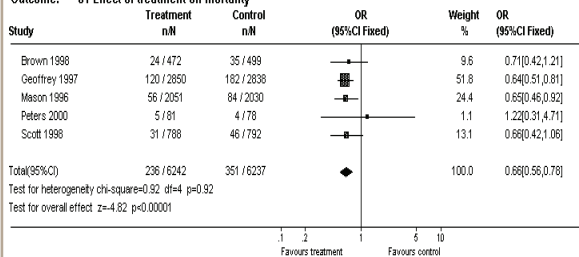
Appendix 5 Presenting the results of a systematic review²⁸ (Example)

How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a **forest plot**.

Comparison: 03 Treatment versus Placebo

Outcome: 01 Effect of treatment on mortality



The forest plot depicted above represents a meta-analysis of 5 trials that assessed the effects of a hypothetical treatment on mortality. Individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment - an odds ratio of 1.0. When the confidence interval includes 1 it indicates that the result is not significant at conventional levels ($P>0.05$).

The diamond at the bottom represents the combined or pooled odds ratio of all 5 trials with its 95% confidence interval. In this case, it shows that the treatment reduces mortality by 34% (OR 0.66 95% CI 0.56 to 0.78). Notice that the diamond does not overlap the 'no effect' line (the confidence interval doesn't include 1) so we can be assured that the pooled OR is statistically significant. The test for overall effect also indicates statistical significance ($p<0.0001$).

Exploring heterogeneity

Heterogeneity can be assessed using the "eyeball" test or more formally with statistical tests, such as the Cochran Q test. With the "eyeball" test one looks for overlap of the confidence intervals of the trials with the summary estimate and whether the point estimates are within the confidence intervals of the estimates of the other studies. In the example above note that the dotted line running vertically through the combined odds ratio crosses the horizontal lines of all the individual studies indicating that the studies are homogenous. Heterogeneity can also be assessed using the Cochran chi-square (Cochran Q). If Cochran Q is statistically significant there is statistically significant heterogeneity. If Cochran Q is not statistically significant but the ratio of Cochran Q and the degrees of freedom (Q/df) is > 1 there is possible heterogeneity. If Cochran Q is not statistically significant and Q/df is < 1 then heterogeneity is very unlikely. In the example above Q/df is < 1 ($0.92/4 = 0.23$) and the p-value is not significant (0.92) indicating no heterogeneity. Heterogeneity can be quantified using the I^2 (Higgins et al) that ranges from 0 to 100%. The higher the I^2 the greater the heterogeneity (i.e. that differences between studies are not likely due to chance).

Note: The level of significance for Cochran Q is often set at 0.1 due to the low power of the test to detect heterogeneity

²⁸ Systematic Review Critical Appraisal Sheet, Centre for Evidence Based Medicine, University of Oxford, 2005. See <http://www.cebm.net/index.aspx?o=1157>.

Appendix 6 Template for implementation plan

| | | | |
|--|---|-------------|--|
| Objective | <i>What needs to be achieved?</i> | | |
| Barriers | <i>A short description of potential barriers to implementation and how to overcome them; potential incentives.</i> | | |
| Key success factors | <i>Achieving main objectives are dependent upon...? What needs to be done?</i> | | |
| | Details | Date | Responsible institution/ person |
| Dissemination | <i>A short description of channels the developer plans to use.</i> | | |
| Launching the guideline to stakeholders | <i>How will the guideline be disseminated, including where, when, and to whom?</i> | | |
| Education and training | <i>A short description of training needs and planned courses and seminars.</i> | | |
| | | | |
| Monitoring | <i>A list of expected process and outcome indicators and evaluation dates, including:</i> <ul style="list-style-type: none"> • <i>Indicators description and audit targets</i> • <i>Standard to be achieved</i> • <i>Baseline assessment</i> • <i>Monitoring and evaluating</i> | | |
| Resources | <i>A list of resources (on a different level) needed for implementation.</i> | | |

