ESTONIAN HANDBOOK FOR GUIDELINES DEVELOPMENT 2020
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The Estonian Adaptation of the Estonian Handbook for Guidelines Development 2011 contains: certain recommendations based on the updates of the international guideline development methods, as well as updates and improvements to the local processes and structures.
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<td>ACE</td>
<td>angiotensin converting enzyme</td>
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<tr>
<td>AGREE</td>
<td>Appraisal of Guidelines for Research and Evaluation</td>
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<td>AHRQ</td>
<td>United States Agency for Healthcare Research and Quality</td>
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<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
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<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<tr>
<td>ARV</td>
<td>antiretroviral</td>
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<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
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<td>BHS</td>
<td>British Hypertension Society</td>
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<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CMA</td>
<td>Competition and Markets Authority</td>
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<td>COI</td>
<td>conflict of interest</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<tr>
<td>CT</td>
<td>computerized tomography</td>
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<tr>
<td>DOI</td>
<td>declaration of interest</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>DTA</td>
<td>diagnostic test accuracy</td>
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<tr>
<td>EHIF</td>
<td>Estonian Health Insurance Fund</td>
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<td>ESH</td>
<td>European Society of Hypertension</td>
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<tr>
<td>EtD</td>
<td>Evidence to Decision (frameworks, tables, summaries)</td>
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<td>EU</td>
<td>European Union</td>
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<td>GAB</td>
<td>Guideline Advisory Board</td>
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<td>GDT</td>
<td>Guideline Development Tool</td>
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<td>GIN</td>
<td>Guidelines International Network</td>
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<td>GRADE</td>
<td>Grades of Recommendations Assessment, Development and Evaluation</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>HTA</td>
<td>health technology assessment</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>ICSI</td>
<td>Institute for Clinical Systems Improvement</td>
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<td>IGRA</td>
<td>interferon gamma release assay</td>
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<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>IT</td>
<td>information technology</td>
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<td>JNC</td>
<td>Joint National Committee</td>
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<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
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<td>MeSH</td>
<td>Medical Subject Headings</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<td>NLM</td>
<td>National Library of Medicine</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PICO</td>
<td>population – intervention – comparator – outcome</td>
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<tr>
<td>RIGHT</td>
<td>Essential Reporting Items for Practice Guidelines in Healthcare</td>
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<tr>
<td>ROBIS</td>
<td>risk of bias in systematic reviews</td>
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<td>RR</td>
<td>risk ratio</td>
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<tr>
<td>SIGN</td>
<td>Scottish Intercollegiate Guidelines Network</td>
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<tr>
<td>SIRU</td>
<td>small informative recommendation unit</td>
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<tr>
<td>SoF table</td>
<td>summary of findings table</td>
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<td>STROBE</td>
<td>Strengthening the Reporting of OBservational studies in Epidemiology</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>VHA</td>
<td>Veterans Health Administration</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Acknowledgements

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Foreword

Health guidelines are universally recognized, which makes them an essential tool in improving the quality of health care and health services provided and in ensuring consistent care of patients with similar diagnoses by all health-care professionals. Several organizations and professional associations are involved in the preparation of guidelines in Estonia and, since 2003, the Estonian Health Insurance Fund commissions guidelines developed by, or with input from, such associations.

In 2010 a comprehensive evaluation and analysis of the practices around developing guidelines in Estonia was carried out. This included a wide-ranging survey of physicians and benefited from the assistance of international experts. Based on the analysis, experts from WHO made suggestions on how to create a more rigorous structure, applying the universal principles for the development of guidelines. The Guideline Advisory Board was established as a result of these suggestions, in cooperation with the Estonian Health Insurance Fund and the University of Tartu, tasked with ensuring the appropriateness and methodological supervision of the guidelines being developed. In conjunction with the establishment of the Guideline Advisory Board, a methodological manual entitled *Estonian handbook for guidelines development* was prepared with the cooperation of WHO, the Ministry of Social Affairs, the Medical Faculty of the University of Tartu, and other parties with a vested interest in the health-care system (1). The next important step was the creation of a dedicated website1 bringing together all the guidelines based on the new methodology, including annexes and source documents.

The guidelines material and information published on the website provide transparency of the process and contribute to its reliability. As such, the website has become an essential tool for the development of guidelines for health-care professionals, facilitating information retrieval. Following the new methodology, between 2011 and the end of 2019, 21 guidelines (along with 17 versions for patients and lay people) have been completed and approved by the Guideline Advisory Board.

In 2015, WHO experts analysed the development of guidelines in Estonia since 2011, acknowledging the institutional structure and methodological support provided in the preparation of guidelines, as well as the substantive work of all participants in their development (2). These experts also acknowledged the fact that, over a period of just a couple of years, more than 200 Estonian health-care professionals

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had been trained under the guidance of the Estonian Health Insurance Fund and with the support of WHO, assuring adherence to the principles of evidence-based medicine in the development of guidelines. The report condensing the findings from the interim appraisal of progress proposed further improvements to the process of guideline development itself, with recommendations including working towards organizational development of guidelines, improvements in methodology, and the updating of guidelines.

Based on the recommendations of the experts, this methodological guide has also been updated; as such, the manual brings together the current experiences from Estonia and internationally recognized current methods for compiling guidelines. It addresses all aspects of guideline development, from assessing the necessity of the guideline to discussing its distribution, implementation and any necessary updating.

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Estonian Health Insurance Fund University of Tartu

Kristina Köhler
Liaison Officer
WHO Country Office in Estonia
1. The purpose and importance of a guideline and its impact on quality of care

Clinical medicine, public health and health policy and the related research are in constant development. More effective diagnostic and care methods are being introduced daily, and old truths sometimes require re-evaluation. In the context of this overload of information, it is difficult and time-consuming to find one’s way in the search for the best solution for each patient, or the population more widely; especially if the information is conflicting, or new information differs from the usual practice.

A guideline is a document that contains systematically developed evidence-based recommendations that assist health professionals and recipients of care to make informed decisions. Recommendations may address clinical, public health, health systems and health policy decision-making (3,4).

As a general rule, guidelines answer questions on one disease or condition while possibly considering multimorbidity and providing guidance on how to prevent, diagnose, treat or improve care for the disease or condition. The main underlying principles for developing trustworthy guidelines are ensuring – throughout the development process – transparency, systematic use of scientific methods and good management of any potential conflict of interest (COI). Guidelines contain recommendations for clinical practice or public health policy. A recommendation tells the intended end-user of the guideline what they can or should do in specific situations to achieve the best health outcomes possible, individually or collectively. It offers a choice among different interventions or measures leading to net positive consequences. Recommendations help the user of the guideline to make informed decisions on whether to undertake specific interventions (including tests), public health or health policy measures, and on where and when to do so. They also help the user to select and prioritize across a range of potential interventions.

Trustworthy guidelines have the potential to reduce inappropriate variations in practices, enhance translation of research into practice, and improve health-care quality and safety (3–8). For ease of reference, Annex 1 provides definitions and explanations of the terms used in this handbook. The main difference between a guideline and other learning material (e.g. a medical textbook) is that guidelines provide answers to foreground questions (e.g. “should all patients use intervention x or y?”) in the format of recommendations. They answer questions about what should or could be done in specific circumstances, while medical textbooks typically focus on the background and how interventions work.
There may be a variety of stimuli for developing a guideline, for example: controversial or new information on the effectiveness of care methods to address the health problem; significant differences in patient care and/or care practices; results from clinical audits; conclusions of a health technology assessment (HTA); feedback from practitioners; the introduction of new interventions or health technologies; problems encountered in a health-care organization, and so on. The Estonian guidelines process will focus on essential situations that need resolving, with a view on priorities for Estonia.

Modern health-care providers and personnel in the health sector work in multi-disciplinary teams, whereby each member contributes their skills to achieving their own tasks. These diverse groups of professionals and patient representatives agree on the development of guidelines and ensure collaboration and division of labour in the specific contexts for which the guidelines are developed. The guidelines developed in Estonia according to this handbook focus on the Estonian health-care setting, with the goal of providing the best possible results for the people of Estonia.

When designing a trustworthy guideline, a specific methodology must be followed to ensure that the resulting guideline recommendations are also trustworthy, based on reliable and up-to-date evidence. They must also be implementable, which requires taking into account the specific country context in terms of the circumstances surrounding the organization of health care, as well as values, and the resources available. Comprehensive and useful guidelines provide the basis for improving the quality of services provided throughout the health-care system; they do this by providing health-care professionals with the necessary decision-making support, improving the use of resources and enabling patients to make more informed choices.

Sometimes there are more suitable opportunities to improve the quality of care; such as regulatory measures, system-based strategies, peer review, training, and so on. Therefore, before developing a guideline, careful consideration should always be given whether a guideline is in fact the best way to achieve the required improvements.
2. **The guideline development process: an overview**

2.1 **How to use this guideline handbook**

This handbook is intended to be an up-to-date practical resource. It is currently made available in English and in electronic format that can be used online or printed as a .PDF document. Derivative products and examples are made available in Estonian and all products of the guideline groups will also be available in Estonian. Future versions (after 2019) of the handbook may be printed and translated to Estonian. The handbook is organized into sections and includes figures and annexes as supporting material. Practical examples will be added online, and the handbook will be updated regularly (indicated by prominently displaying the date of the latest available version). The handbook is intended for those who need to apply the processes, and/or those who want to develop an in-depth understanding of the Estonian guideline process, as well as those who wish to apply it to their settings.

2.2 **The guideline development process in Estonia**

The process of guideline development should be transparent, well thought-out and carried out in close cooperation with all relevant parties including the relevant health-care professionals, patients, and the public. This process does not end with the approval of the guidelines. It is also essential to draw up an implementation plan for the guidelines, together with measurable outcomes, to assess the achievement of the goals set.

The Estonian Health Insurance Fund (EHIF) has been the main funding body for the development of guidelines since 1998, and since 2011 it has been guided by the Guideline Advisory Board (GAB), the composition of which is determined thorough cooperation between the EHIF and the University of Tartu. The parties, stages and specific tasks involved in the development of a guideline are described in Fig. 2.1. The entire process of guideline development and management – as well as implementation – are carried out using the GRADEpro\(^2\) Guideline Development Tool (GDT) (9).\(^2\)

The development of guidelines may be organized and funded by another organization or institution, but if the guidelines are to be acknowledged as trustworthy they need to be approved by the GAB, and formulated in accordance with the principles and methodology presented in this handbook, including disclosing the interests of

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\(^2\) GRADE: Grading of Recommendations Assessment, Development and Evaluation GRADE working group. GRADEpro GDT [website]. Hamilton (ON): McMaster University; 2015 (http://gradepro.org/).
the parties and ensuring the appropriate resolution of any potential COI.

Development of a guideline is usually initiated by an association of health-care professionals or other organizations (such as a patient association, or educational institution). The initiator submits to the GAB a proposal for guideline development, along with the initial scope (known as the topic proposal). The GAB consists of experts who: choose appropriate and important topics for guideline development from among those raised on an annual basis; confirm panels and secretariats for the guidelines that are to be prepared; monitor the development of guidelines; and approve the completed guidelines.

Guideline development is coordinated by the Guideline Unit at the University of Tartu (established in June 2018), which provides the required methodological and technical-administrative support to guideline developers; namely, the Guideline Panel and the Guideline Secretariat.

**Fig. 2.1. The process of guideline development**

Notes. This figure presents the process used in the Estonian guideline development process. The GAB and the Guideline Unit at the University of Tartu have general oversight of the organization, budgeting, planning and training. The GAB determines any COI and manages the membership of the Guideline Panel. Funding is provided by the EHIF. The Panel formulates the questions, and the Secretariat prepares the evidence, both supported by the Guideline Unit. The Panel is responsible for developing the recommendations. The EHIF is responsible for dissemination, implementation, quality improvement activities and evaluation of the impact of guidelines.

*Source: GRADEpro GDT (2015) (9).*
The Panel, approved by the GAB, draws up the final scope of the guideline and submits it to the GAB for approval before commencing the process of developing recommendations for the guideline. If there is a need to change the scope of the guideline in a significant way during the process of guideline development, a proposal to that effect should be submitted to the GAB.

Guideline recommendations are formulated by the Panel according to the evidence synthesis prepared by the Secretariat. In order to ensure the quality of the guidelines produced, it is mandatory for any members of the Panel and the Secretariat without previous experience in developing guidelines to undergo appropriate training before starting the work. The process of developing guidelines and managing any COI, as well as the decisions made are all documented.

During or at the end of the guideline development process, an implementation plan, a patients’ version of the recommendations and (if necessary) other patient information materials are initiated. The patients’ version is a tool designed for independent use by lay people or patients; it should include explanations of the guideline recommendations in a way that is accessible to lay people, for ease of understanding.

The completed guideline is to be submitted to the GAB for approval. Prior to final approval, the GAB must ensure that the guideline developers followed the required methodology and process. They must also ensure that the guidelines undergo a review. The approved guidelines, along with their annexes, are published on the website.²

3. The GAB and the Guideline Unit

The core structures for the Estonian guideline development enterprise are the GAB and Guideline Unit at the University of Tartu. The GAB was established in 2011 to provide oversight and stewardship in guideline development. Since 2018 the Guideline Unit operates under the Faculty of Medicine of the University of Tartu and ensures methodological and administrative support; activities that were previously undertaken by the EHIF.

3.1 Tasks of the GAB

The aim of the GAB is to steer the development and implementation (and ensure the quality) of evidence-based, trustworthy and implementable Estonian guidelines that take into account the Estonian context and people’s preferences and values.

The GAB:
- approves the methodology for the preparation of guidelines (that is, this handbook);
- selects from the presented topic proposals the topic(s) for guideline development, supported by the Guideline Unit and included in the work plan for activities that are supported by the EHIF;
- decides on the updating of guideline(s) based on the recommendations of the Guideline Unit;
- confirms the final scope of the guideline submitted by the Panel;
- discusses and approves the composition of the Panel for any guideline to be developed, along with the chairs and members of the Secretariat for each guideline;
- evaluates any declaration of interest (DOI) and manages any COI of the members of the GAB, the Panel and the Secretariat;
- approves the work plan (including timetable) for the development of the guideline;
- considers the interim report presented by the Chair of the Panel on the development of the guideline and provides advice on further improvements;
- selects the reviewers for the guideline;
- approves the final recommendations, along with the implementation plan and, if applicable, the patients’ version;
- assesses performance of the implementation plan.

The GAB will meet as required, but it should convene in person at least four times a year. The following activities take place during these meetings as necessary: guideline development methodology is approved; the topics for the guidelines to be developed are decided; the completed guidelines are approved; progress of the guidelines being developed is monitored; advice is given where necessary on the
development of a guideline (or the patients’ version thereof); and the implementation of completed guidelines is monitored.

3.2 Composition of the GAB

The GAB consists of representatives of various educational and research institutions, professional associations and other organizations, as well as individuals representing patients or lay people. The members of the GAB are expected to have experience in developing guidelines but, in the absence of such experience, any new member of the GAB should undergo training and participate in the preparation of at least one guideline.

The GAB is chaired by a person in the field of medical sciences, appointed by the Dean of the Faculty of Medicine at the University of Tartu. The main and the stand-in members of the GAB are nominated by the Dean for a period of three years, according to the proposals of the following organizations:
- Estonian Medical Association
- Family Physicians Association of Estonia
- Estonian Nurses Union
- Estonian Hospitals Association
- Estonian Chamber of Disabled People
- University of Tartu Institute of Clinical Medicine
- University of Tartu Institute of Family Medicine and Public Health
- National Institute for Health Development
- State Agency of Medicines
- Ministry of Social Affairs
- EHIF
- Health Board
- various higher education institutions in the field of health care.

3.3 Guideline Unit (at the University of Tartu)

The Guideline Unit is the team supporting the GAB, as well as the teams developing the guidelines (both the Panel and the Secretariat). The Panel and the Guideline Unit collaborate to ensure the trustworthiness of the guidelines’ content, consistent with the principles of evidence-based health care and the methodology agreed on in this handbook. The Guideline Unit ensures the reliability and transparency of the process leading to their development, following the GIN-McMaster\(^4\) Guideline Development Checklist.\(^5\) This is included in GRADEpro, which is the tool used

\(^4\) GIN: Guidelines International Network.

\(^5\) https://heigrade.mcmaster.ca/guideline-development/using-checklist
by the Guideline Unit and the Panel to develop recommendations and support their implementation (Fig. 3.1) (8,9).

**Fig. 3.1. Using the GIN-McMaster Guideline Development Checklist and GRADEpro in guideline development**

Note. The checklist allows planning of the process and the development of the guideline itself, as well as dissemination, and is included in the GRADEpro GDT.


**Competences of the Guideline Unit include:**
- evidence-based medicine;
- epidemiology and biostatistics;
- literature search and primary review;
- methodology of preparing systematic reviews;
- information technology;
- medical writing;
- communication.

Administrative, technical and organizational tasks of the Guideline Unit include:
- counselling the health professionals and health system officials before preparing topic proposals;
- organizing the presentation of topic proposals and the involvement of interested parties;
- proposing a list of Panel members, upon consulting the person/institution that prepared the guideline proposal and relevant professional organizations;
  - compiling the Secretariat, upon consulting the Panel and the head of the Secretariat;
- arranging the meetings of the GAB, preparing the agenda and drawing up the minutes;
- organizing the tasks for the panels and secretariats, including meetings (and preparation between the meetings);
- managing submissions of DOI and documenting the resolution of any COI;
- organizing remuneration for the work of the members of the panels and secretariats according to their contribution;
- providing content for the website (however, the administration of the website is the responsibility of the EHIF);
- ensuring the archiving of key documents for the development of approved guidelines (including tables depicting the preparation of summaries of findings/evidence and recommendations) and the scientific literature used.

Methodological tasks of the Guideline Unit include:
- determining the person in charge of developing each guideline from among its staff;
- providing methodological advice and support to panels and secretariats in the development of the guideline implementation plan, including in the search for scientific literature, appraisal and synthesis of evidence, and formulation of recommendations (if needed, taking a methodology-focused co-Chair role on the Panel (see section 4.1 on the composition and chair(s) of a Panel));
- carrying out the training for the individuals developing the guidelines;
- submitting to the GAB a proposal regarding the appointment of a reviewer for each guideline being developed;
- ensuring guidelines are developed in accordance with the correct methodology, as well as their timely completion;
- evaluating the need to update the guidelines.

The work of the Secretariat of each guideline is overseen by one or two members of the Guideline Unit, operating as guideline development methodologists, ensuring that the guidelines are developed in accordance with the methodology and principles agreed upon in this handbook.
4. The Guideline Panel and the Guideline Secretariat

There are two key groups set up specifically for the development of each guideline: a Panel and a Secretariat. The Panel (approved by GAB) is responsible for the development of the guideline in close collaboration with the Secretariat, which prepares evidence for the formulation of relevant recommendations.

It is mandatory for any members of the Panel and the Secretariat without previous experience in developing guidelines (in accordance with this handbook) to undergo training in appropriate methodologies before embarking on guideline development.

4.1 Composition and Chair(s) of a Panel

Panels include the following members: health professionals with content knowledge, patients or patient representatives (or other lay people), methodology experts, and individuals with relevant expertise (e.g. in economics).

The Panel must represent a balance of the various health-care levels (primary care, hospital care, nursing care) according to the topic. It monitors the regional representation of experts and involves health professionals whose work will be most affected by the guideline. Panel members represent their own views and not those of organizations, although they may be recruited from or suggested by these organizations. The optimal Panel size is 8–10 members, but depending on the guideline topic and target group, it may be necessary to involve fewer or more members and to invite consultants for their input on individual issues.

The guideline topic initiator may submit a proposal to the GAB on the possible composition of the Panel and on nominating a candidate for Chair of the Panel (the chair and co-Chair are selected by the GAB). The GAB assesses the competences of the parties represented in the Panel and may submit further proposals regarding its composition. One or two Guideline Unit members are assigned to each guideline. These Guideline Unit members will be responsible for consulting the person/institution that prepared the guideline proposal and relevant professional organizations, as well as for compiling a list of Panel members. As mentioned above, the Guideline Unit is responsible for compiling the Secretariat, consulting the Panel and the Head of the Secretariat.

The members of the Panel and the required competences include the following groups of stakeholders (this list is not exhaustive).
✓ **Content experts** should be included, who represent the perspective(s) of health-care and social-care professionals (as well as other types of health professional, 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**, as experts in assessing health 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 guide not only the Panel in understanding evidence but also the process of formulating recommendations. The guideline methodologist should have experience that is consistent with the aspects in guideline development highlighted in blue and green in Fig. 4.1.6

✓ **Public or patient representatives** from patients’ organizations or a representative of the patient with the relevant chronic condition should also be involved as Panel members to represent the view of the patient(s).

✓ **The relevant medical faculty(ies) from a university** should be included to support educational activities and implementation (organized by the EHIF).

✓ **Managers and other health professionals** should be included to provide expert opinion on the implementation of guidelines from the point of view of healthcare services provision.

✓ **Health economists or biostatisticians** may be included/consulted to provide an analysis of the costs of health services, cost–effectiveness, data on the provision of health-care services and medicines, and so on.

### 4.1.1 Chair(s) of a 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 not only knowledge of the content, but also 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 Guideline Panel.

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6 McMaster University’s [inguide.org](http://inguide.org) website also provides further information on training for guidelines development.
Fig. 4.1. Core steps in guideline development based on the guideline checklist

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Organization, budget, planning and training</td>
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<tr>
<td>2.</td>
<td>Priority-setting</td>
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<tr>
<td>3.</td>
<td>Guideline group membership</td>
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<tr>
<td>4.</td>
<td>Establishing guideline group processes</td>
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<tr>
<td>5.</td>
<td>Identifying target audience and topic selection</td>
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<tr>
<td>6.</td>
<td>Consumer and stakeholder involvement</td>
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<tr>
<td>7.</td>
<td>COI considerations</td>
</tr>
<tr>
<td>8.</td>
<td>(PICO) question generation</td>
</tr>
<tr>
<td>9.</td>
<td>Considering importance of outcomes and interventions, values, preferences and utilities</td>
</tr>
<tr>
<td>10.</td>
<td>Deciding what evidence to include and searching for evidence</td>
</tr>
<tr>
<td>11.</td>
<td>Summarizing evidence and considering additional information</td>
</tr>
<tr>
<td>12.</td>
<td>Judging quality, strength or certainty of a body of evidence</td>
</tr>
<tr>
<td>13.</td>
<td>Developing recommendations and determining their strength</td>
</tr>
<tr>
<td>14.</td>
<td>Wording of recommendations and of considerations of implementation, feasibility and equity</td>
</tr>
<tr>
<td>15.</td>
<td>Reporting and peer review</td>
</tr>
<tr>
<td>16.</td>
<td>Dissemination and implementation</td>
</tr>
<tr>
<td>17.</td>
<td>Evaluation and use</td>
</tr>
<tr>
<td>18.</td>
<td>Updating</td>
</tr>
</tbody>
</table>

Notes. PICO: population – intervention – comparator – outcome. There are 18 core areas for guideline development as per the GIN-McMaster Guideline Development Checklist (https://heigrade.mcmaster.ca/guideline-development/using-checklist) that was developed in conjunction with the Estonian Guidelines programme. The blue areas describe the basic competences on which any Guideline Panel member should receive training. The green areas describe the additional competences of the guideline methodologist, and the orange fields detail the competences of the guideline (method-orientated) co-Chair.

Source: Schünemann et al. (2014) (8).

The selection of a co-Chair to cover certain relevant aspects may be appropriate; a Panel may be chaired jointly by a methodologist (from the Guideline Unit) and a content expert, who may agree together how to manage the meetings as co-chairs. Panel chairs should use the Panel Chair checklist (see Annex 2). If included, the (methodologist) co-Chair may be a member of the Guideline Unit,
and may or may not be involved in the preparation of the evidence synthesis summaries and Evidence to Decision (EtD) frameworks. This person will, in collaboration with the content-focused co-Chair, ensure objectivity and compliance to the methodology throughout the meetings.

The primary task of the Chair(s) of the Panel is to lead the Panel meetings, facilitate reaching a formal consensus on evidence-based recommendations, and present the guideline for approval. The factors and tasks for the Chair(s) to consider are presented in the Guideline Panel Chair checklist (Annex 2). 7

In addition to managing the process of guideline development, the Chair(s) of the Panel is (are) also expected to participate in the development of an implementation plan for the guideline and to support the presentation of the guideline to the target group.

4.1.2 Tasks of a Panel

The Panel formulates the guideline scope and recommendations, presents the interim progress report to the GAB, approves the final guideline, and submits it to the GAB for approval. The Panel then introduces the guideline and contributes to its implementation (also developing, if needed, the patients’ version of the guideline and other derivative materials).

The Panel must comply with the current Estonian guidelines development methodology (described in this handbook). It is required to ensure that the underlying evidence supporting specific recommendations is carefully assessed; and that patients’ values and preferences, along with the implementation of the recommendations, align appropriately with local circumstances and take into account the structure and capacity of the Estonian health-care system.

4.1.3 Members of a Guideline Panel

The role of members of a Panel is to:
- participate in training to convey knowledge on how to carry out tasks in accordance with the role of developing guidelines and recommendations, and assuring quality of developing guidelines;
- participate in the meetings of the Panel to actively contribute to the development of the guideline, as well as to ensure the evidence-based nature of the recommendations and the suitability for implementation within the Estonian health-care system.

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7 https://heigrade.mcmaster.ca/guideline-development/chair-checklist
setting (see Annex 3 for the Guideline Participant Tool for group meeting participants);
- formulate health questions, select outcomes, and submit the scope of the guideline for approval to the GAB;
- if necessary, request the presence of a specialist consultant for involvement in discussions on a specific issue;
- work with the Guideline Unit and the Secretariat on specific questions and recommendations to complete EtD frameworks and present the information to the rest of the Panel;
- work through the material prepared by the Secretariat and submit it at the meeting (or before the meeting in writing, if unable to attend);
- review recommendations, drafted by the Secretariat, according to the processes set out here;
- determine the strength of the recommendations, taking into account the assessment of the evidence using the GRADE method (10,11);
- review feedback and suggestions received during the review of the recommendations or guideline, the feedback received from other parties, and changes to the guideline prepared by the Secretariat;
- agree on the activities for implementing the guideline, along with the indicators for assessing its implementation;
- approve the completed guideline (including the patients’ version), together with the implementation plan, submit it for approval to the GAB, and contribute to its implementation.

4.2 Composition and tasks of a Guideline Secretariat

A separate secretariat for each guideline is assigned by the Guideline Unit in agreement with the GAB and the Chair of the Panel. The primary task of the members of the Guideline Secretariat is to collect and evaluate scientific evidence and to produce a summary of that evidence. If a member of the Secretariat does not have the necessary experience, they must first undergo appropriate training.

The optimal size of a secretariat is 5–6 members, but this can be adjusted depending on the guideline topic. The majority of the members of the Secretariat should have the appropriate experience to complete the task. The work of the Secretariat is overseen by 1–2 members of the Guideline Unit, whose task is to ensure the guideline is consistent and in accordance with the principles agreed upon in this handbook.

The work of the Secretariat is supported by the Guideline Unit, assisting in the search for and systematization of evidence, as well as in the organization of meet-
ings and documentation of the decision-making processes.

4.2.1 Head of the Secretariat

In order to ensure the efficient functioning of the Secretariat, it is essential that its head is familiar with the guideline development methodology and has experience in developing guidelines in accordance with that methodology (including the necessary skills for finding and evaluating evidence).

If the expert members of the Secretariat have no relevant experience in developing guidelines, a member of the Guideline Unit may also be appointed as head of the Guideline Secretariat. A candidate for the position is submitted by the guideline topic initiator and the Chair of the Panel for approval. The primary task of the head of the Secretariat is to ensure the guideline is developed in accordance with the principles and methodology set out in this handbook and following the evidence-based nature of the recommendations. The Guideline Unit interacts with the head of the Secretariat and organizes smooth exchange of information with the Panel, the GAB and any third parties involved.

4.2.2 Members of the Secretariat

The role of members of a Secretariat is to:
- participate in training to assure the quality of guideline development;
- participate in the meetings of the Panel;
- assist in drawing up the final scope of the guideline;
- establish a work plan for the development of the guideline, the patients’ version and other derivatives and related materials, after approval of the scope of the guideline;
- develop a strategy for finding scientific evidence and a summary description of the search and selection process;
- identify health questions that require economic analysis in order to make a recommendation;
- seek and systematize evidence, and compile evidence summaries and tables based on the EtD frameworks, demonstrating the path from evidence to recommendations;
- evaluate existing guidelines and evidence with the help of various tools, including Appraisal of Guidelines for Research and Evaluation (AGREE) II; ROBIS (a tool to assess risk of bias in systematic reviews); the GRADE approach; and, in particular, the GRADEpro tool;
- draw up draft recommendations for answering health questions;
- in collaboration with the Panel, write the first version of the guideline and the
implementation plan;
- review feedback, evaluate the reviews submitted on the working version of the guideline, and make proposals to the Panel on any amendments to the guideline;
- in line with the guidelines and the agreements of the Panel, develop the final text of the recommendations and make suggestions for the implementation plan.

4.3 Training for the members of the Panel and the Secretariat

Following the approval of the members of the Panel and the representatives of the Guideline Unit by the GAB, any appointed members without prior experience of developing guidelines (according to this handbook) will undergo guideline training coordinated by the Guideline Unit or the EHIF. The aim of the training is to ensure that all members of the guideline development groups have the relevant competences, according to Fig. 4.1, in order to assure the quality of guideline development.

The training includes:
- information on the process of developing guidelines;
- guidance on developing the scope, including formulating health questions (in population–intervention–comparator–outcome (PICO) format; see section 6.4) and organizational health care-related issues;
- understanding the PICO format for health questions, including the selection of outcomes;
- an overview of the methods for searching and evaluating evidence. This overview includes:
  • establishing what makes a guideline credible (Institute of Medicine (IOM) standards (6) and AGREE II (5));
  • understanding the principles of systematic reviews and meta-analyses;
  • understanding the critical criteria for developing a recommendation based on the available evidence (including the impact on resources, applicability, values and preferences, and balance of harms and benefits) based on the evidence using GRADE EtD frameworks (see Annex 4);
  • receiving information on how to use the relevant electronic tools, including email responses to invitations from Doodle (scheduling), Skype (attending meetings), GRADEpro and PanelVoice (input and voting on recommendations), and OneDrive (file sharing).
5. DOI, resolution of any COI, and confidentiality

Members of the Guideline Panel and other groups involved in guideline development should be impartial, independent and objective. When developing guidelines, it is essential to avoid situations where the various interests can unduly influence the work of the GAB, the Panel or the Secretariat, and thus undermine the credibility of the guideline recommendations and jeopardize implementation.

A COI is “a divergence between an individual’s private interests and his or her professional obligations such that an independent observer might reasonably question whether the individual’s professional actions or decisions are motivated by personal gain, such as direct financial, academic advancement, clinical revenue streams, or community standing” (12).

According to WHO, a DOI is the disclosure of any potential or actual COI that includes 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 DOI must also include any relevant interests of others who may, or may be perceived to, unduly influence the expert’s judgement, 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. Any DOI should be carried out according to the forms approved by the GAB and in this handbook (see Annex 5) (13).

A DOI indicates a GAB, Panel, Secretariat and Guideline Unit 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 COI 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 the following conditions are observed.

- Each Panel member, including the Chair, the nominated Guideline Unit member, and consultant (if involved), should complete and submit a DOI to the GAB (see Annex 5). The GAB then decides whether the declaration contains any conflicts that should result in the exclusion of a proposed Panel member.

- At the first Panel meeting, and at all subsequent meetings, each Panel member should verbally report any potential COI. All Panel members and any individuals who have direct input into the guideline (e.g. consultants) 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. The Panel Chair is
responsible for ensuring this is done. If a member has a (new) COI, several possibilities exist. First, the member may be invited to participate, but only if their conflict is publicly disclosed. Second, the member 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 member may be asked to withdraw from the Panel entirely.

Additionally, Secretariat members (including the head of the Secretariat and the nominated Guideline Unit member) are each required to complete and submit a DOI. The same rules about any DOI or COI apply to them as to the Panel members.

The main categories of interest that are subject to declaration are:
- financial interests in pharmaceutical and medical companies (ownership, shares);
- work carried out for pharmaceutical or device companies (permanent or temporary work, consultancy/expertise provided);
- other relationships with pharmaceutical or device companies (scholarships, research grants, sponsorship);
- relationships with other businesses related to the guideline topic (e.g. IT companies);
- personal non-financial interests (that is, having taken a position on the health question(s) of the guidelines that could impede objective assessment of the evidence).

The DOI will be updated if any new interests emerge, on an ongoing basis during the guideline development process. Any COI must be reflected in the guideline development documentation, with an explanation of what each conflict constituted and how it was managed.

In addition, Panel members and others involved in the guideline development process should commit to keeping all information confidential unless permission has been obtained from the GAB or the information disclosed is in the public domain.
6. Topic proposals and preparation of the scope

A guideline topic 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. The topics to be drafted for the guidelines are decided by the GAB from among the topic proposals submitted within the timeline set by the GAB and the EHIF, and based on the criteria outlined for them (see annexes 6–9). The GAB evaluates the proposals submitted and selects the priority topics.

The scope of the guideline defines the topics for guideline development, specifying the content of the health problem to be addressed and the level of care required. This informs the formulation of the clinical and, where appropriate, health organization-related issues, the solutions to which are intended to be found in the guideline in the form of recommendations. The distinction is made between the initial scope (topic proposal) and the final scope (confirmed by the GAB), as detailed in the sections of this handbook that follow.

6.1 Proposing a topic for the guideline

Proposals for developing guidelines can be submitted by various actors. The GAB can declare nationally important topics for guideline development, for which topic proposals can then be presented. They can also be submitted by specialist associations; professional associations of health-care workers; health-care providers; and educational facilities and other interested parties, including the EHIF, departments of the University of Tartu and other educational institutions working in the field of medical sciences, along with various national authorities (such as the National Institute for Health Development, the Ministry of Social Affairs, and the Health Board). Owing to a significant COI, proposals made by companies that manufacture or represent medicinal products or medical devices are not accepted.

The topic is proposed, together with an initial description of the scope, and submitted to the GAB using the relevant forms (see annexes 6 and 7). The topic proposal is to be submitted no later than 1 October each year, with a decision about the accepted proposals anticipated in December. For updates, the deadline for submission is 1 May, and the GAB will decide in the meeting following the submission deadline.

Prior to submitting a topic proposal, appropriate professional associations and the Guideline Unit member should be involved at the earliest possible stage in order
to ensure a coherent understanding of the need for the guideline and readiness for cooperation at a later stage. The submitted document must contain statistical data justifying the choice of topic, which requires the initiator to actively engage with applicable parties (including the Guideline Unit) for input and methodological guidance on developing the topic proposal.

The topic proposal for a guideline (the initial scope) identifies the following aspects:
- a rationale – that is, an explanation to justify why an Estonian guideline is needed, including links to existing relevant guidelines;
- the burden of (the relevant) disease in Estonia;
- the differences in treatment practices and/or health outcomes and/or costs;
- the expected impact on patient health indicators and/or the use of resources;
- patients/target group(s) (e.g. specific age groups or people with a specific illness);
- the level of medical care (primary, specialist or allied health medical care) and the primary users of the guideline;
- clinical issues or problems that need to be addressed in practice;
- professional associations involved in the guideline development process;
- topics not addressed in the guideline;
- contact details of those involved in the topic proposal.

6.2 Selecting topics for guideline development

The members of the GAB evaluate the topics based on the information provided in the initial scope, according to their relevance and the expected benefits. In addition, the potential impact of the implementation of the guideline on resource use and health-care management is taken into account. A topic describes the general area of the guideline (e.g. HIV treatment in children), while the scope describes the guideline questions that will be asked within the topic (e.g. 10 PICO-type (“should”) questions about different interventions for HIV treatment in children); the systematic reviews address the PICO questions (e.g. “what is the impact of HIV treatment xx compared to no HIV treatment xx/HIV treatment xy on the following outcomes?”) and the recommendations provide the answers to the “should” (PICO) questions.

The needs of interested parties should also be taken into account, along with existing evidence-based guidelines that can be adapted or used to prepare a new guideline. The criteria detailed in the handbook subsections that follow should guide the evaluation (see also the examples given in Annex 8).
6.2.1 The problem statement and the purpose of the guideline

Considerations must include the link between the topic and national health-care priorities, and/or the relevance of the guideline.

6.2.1.1 Burden of disease in Estonia
- It is important to consider the size of the patient/target group(s) affected by the disease or condition in Estonia (morbidity, prevalence, mortality, etc.).
- The impact of the disease or condition on the Estonian health and social care system should also be taken into account.

6.2.1.2 Differences in practice and/or health outcomes and/or costs
- Significant differences exist in practices and between/within patient groups (including subgroups); by health-care providers and/or different levels of care (e.g. primary care versus specialist medical care); in different regions of Estonia; or by different cost categories (medicinal products, inpatient treatment, etc.).
- Differences also exist between Estonian and international practices.

6.2.1.3 Expected impacts on patient health indicators and/or use of resources
Anticipated impacts include:
- modernizing current practices;
- introduction of new interventions (including diagnostic and other tests and health-care services);
- availability of new evidence-based practices, possibly altering current practices;
- more efficient use of resources.

6.2.2 Evaluation by the GAB

The GAB is not obliged to choose topics from among those that are proposed, particularly if they are not suitable for the development of the guideline; for example, where there is no need for such a guideline (on that particular topic) in Estonia, or if the new guideline would not lead to changes in practice. It is important to note that issues around the feasibility of creating a guideline may dictate the choice. For example, if a highly credible guideline exists that can be adapted or adopted, then this may present a reason for choosing that guideline. Ideally, those that propose topics should provide information as to whether such guidelines already exist (see subsection 8.1.1 on adolopment).
The GAB documents the reasons for choosing or dismissing each topic and will respond to the topic initiator with a decision, including possible suggestions for improvement. Topics that are not selected may be resubmitted for consideration (according to the timeline set out in the response by the GAB), provided the proposal is updated and amended as needed, based on the feedback received.

If a topic is chosen, the GAB discusses the composition of the Panel and the Secretariat and selects the possible Chair(s) once they have been nominated. Important stakeholders are kept informed about the choice of the topic through announcements on the guidelines website.

6.3 The scope of a guideline

The scope of a guideline determines the boundaries required to prepare it, specifies the content of the health problem to be addressed (e.g. treatment of hypertension, or care of a bariatric patient) and the level of care involved (e.g. family medicine, specialist care), and formulates the issues to be addressed by the guideline.

The distinction is made between the initial scope (topic proposal) and the final scope (confirmed by the GAB). The initial scope is prepared by the topic initiator and the final scope is developed by the Panel, together with the Secretariat and Guideline Unit.

Based on the topic proposal, the Panel, together with the Secretariat, finalizes the scope, which:
- provides an overview of what the guideline contains (e.g. pain relief in the case of lung cancer) and what it does not (e.g. chemotherapy to treat lung cancer), as well as defining the population groups that are included and those that are excluded;
-formulates the title of the guideline and identifies the key questions (clinical and health-care organization-related questions) in PICO format (see section 6.4 on formulating questions);
- sets clear boundaries for the guideline development process so that the work focuses on agreed outcomes, and chooses and evaluates outcomes for this purpose;
- ensures that the guideline is of a reasonable size and is prepared within the prescribed time frame;
-helps to establish whether guidelines exist on the same topic in Estonia or if there is any other up-to-date, relevant evidence.
A guideline should address 10–15 questions. Panels should consider publication and dissemination plans early in the process, as this may help to refine the areas covered. For example, they may plan to publish a guideline in a peer-reviewed journal focusing on diagnosis of a disease before therapy, and this requires discussion early in the process of defining the scope of a guideline. However, rapid dissemination of the work creates satisfaction among those organizing and creating the guidelines (14,15). In addition, those demanding answers and those backing/funding the guideline are usually interested in rapid responses.

Thus, when the Panel has created recommendations during the guideline development process and when they have been approved by the GAB, they could be made available in small informative recommendation units (SIRUs). SIRUs cover a topic without causing confusion or significant gaps, and can stand alone without the full guideline being completed (e.g. a section on diagnosis can be completed before therapy-related questions are discussed and agreed). Confusion and gaps from publishing recommendations can arise if individual recommendations remain uninformative, because they depend on other recommendations, or do not provide key information that is relevant to address a topic (14,15). For example, recommendations in a SIRU about screening among women for breast cancer may be ready for dissemination before the Panel completes other recommendations on the topic of breast cancer diagnosis (15). The number of recommendations in a SIRU is typically 1–4. Understanding and rapidly disseminating SIRUs on the guidelines website avoids the long delays that can occur while guideline groups wait for the approval of an entire guideline document (including all recommendations). This approach allows for rapid feedback by patients, health professionals and policy-makers. It also supports maintaining SIRUs in a live or updated format, where required. These recommendations can be published on the website sooner after approval than full documents. They will require the same approval processes, but the review will take less time because the amount of information is reduced. While preparing the scope it is useful to think of these SIRUs as existing in addition to the publication and dissemination plans for the whole guidance document.

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6.4 Formulating questions for the scope

The scope of the guideline consists of health questions (following the PICO format) to be answered by the guideline. The questions, with outcomes, determine which data should be included and excluded, and what kind of information is to be searched for and evaluated. The questions will later form the basis for developing the guideline recommendations.

It is therefore important that the questions are clear and well-defined, and that there is agreement about them among Panel members. The part of GRADEpro (9–11) that addresses the scope can be used to define it and to brainstorm questions.

The choice of questions to be addressed in a guideline should be based on clinical and policy needs, and on the information provided by experts. Contributions of the target group, patients and/or patient associations may also be helpful. In general, issues should focus on areas that have created controversy or where policies or practices need to be changed. To facilitate this work, information and questions should be initially classified into three main groups, as described in the subsections that follow. However, questions may and should be informed by what information is available from existing credible systematic reviews and guideline recommendations (see subsection 8.1.1 on adolopment) in order to create efficiency in the Estonian guideline process. Chapter 8 of this handbook returns to this, while the following subsections focus on what is known about formulating guideline questions.

6.4.1 Definition and background questions

Background information helps to describe the context of the problem and provides information about the factors that will formulate the PICO question. The following example questions help to establish background information.

- What are the risk factors for HIV infection?
- What are the anatomical causes of low back pain?
- What is the epidemiology and what are the types of atrial fibrillation?
- What terminology is used in management of alcohol use disorder?
- Define what constitutes alcohol use disorder (Diagnostic and Statistical Manual of Mental Disorders (DSM)-5; International Classification of Diseases (ICD)-11), along with its prevalence and treatment options.
6.4.2 Foreground questions

As described earlier, the guideline questions are PICO-format “should” questions about different interventions (including tests and complex interventions) for a specific population. Systematic reviews address the PICO questions in terms of health outcomes (16). Table 6.1 provides a structure and example for the questions, including those that are formulated to inform other EtD criteria. Table 6.2 describes considerations for formulating PICO questions. A recommendation provides the answers to the “should” questions. These answers are a result of evaluating research evidence on the EtD criteria. It is noteworthy that for any of the research evidence sections of the EtD criteria, systematic reviews are the ideal form of knowledge synthesis to inform the guideline question and recommendation. Examples include those listed here.

- Guideline question: should all patients with a suspected sleep-related breathing disorder complete the sleep-related breathing disorder questionnaire in order to be diagnosed (or not)?
- Guideline question: should all patients suspected to have alcohol use disorder be screened (or not) in order to enable planning of interventions for alcohol misuse?
- Guideline question: should pre-exposure prophylaxis be used (or not) to prevent HIV infection among all HIV-negative people belonging to the risk group?
- Guideline question: should a national hypertension screening and treatment programme be used/implemented in Estonia for the whole population?
- PICO question for systematic review or HTA: in the Estonian general population, what is the effect of implementing a national hypertension screening and treatment programme compared to not implementing an organized approach on mortality, stroke, and myocardial infarction?
- PICO question for systematic review or HTA: what is the impact of the introduction of a perioperative safety checklist (as compared to not using such a checklist) on the incidence of complications, the length of hospital stay, mistakes made by staff, and cost?
- PICO question for systematic review or HTA: what is the impact on health outcomes of echocardiography in patients with atrial fibrillation?
- PICO question for systematic review or HTA: what is the effect on patients with venous thrombosis of home treatment versus hospitalization, in terms of mortality, pulmonary embolism, reoccurrence, burden, and pain?
- PICO question for systematic review or HTA: in patients with sepsis or septic shock and increased serum lactate concentration, what is the impact of treatment to normalize serum lactate levels on mortality?
- Foreground question for systematic review: what is the acceptability and feasibility of introducing a perioperative safety checklist in Estonia?
Table 6.1. Description and examples of the PICO method

<table>
<thead>
<tr>
<th>Patient/target group (Population)</th>
<th>Intervention(s)</th>
<th>Comparative intervention(s) (Comparator)</th>
<th>Expected outcomes (Outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which patients/target groups (including subgroups) are involved?</td>
<td>Specific intervention(s)</td>
<td>Compared to another intervention or non-intervention or normal practice</td>
<td>The benefits and harms to the patient’s health as a result of the intervention and/or other potential effects</td>
</tr>
<tr>
<td>In adult patients (&gt; 18 years) and elderly patients (&gt; 75 years) with hypertension ...</td>
<td>... does reducing the amount of salt intake</td>
<td>... compared to the unlimited salt intake</td>
<td>... lower blood pressure and reduce mortality within two years?</td>
</tr>
<tr>
<td>In a patient with bed sores ...</td>
<td>... does using an antiseptic or saline solution</td>
<td>... compared to using pure water to clean the bed sores</td>
<td>... affect the healing of the sore/skin irritation?</td>
</tr>
<tr>
<td>In a patient with sepsis/septic shock...</td>
<td>... does starting antimicrobial therapy within 1 hour of recognizing the disease</td>
<td>... compared with later</td>
<td>... reduce mortality?</td>
</tr>
<tr>
<td>In all patients with suspected pulmonary tuberculosis (TB)...</td>
<td>... do Mantoux and/or interferon gamma release assay (IGRA) testing</td>
<td>... compared to radiological examination and biological material testing</td>
<td>... provide accurate results?</td>
</tr>
<tr>
<td>For all patients with anxiety disorders, for which the medicinal product (monotherapy) prescribed as the first choice is not efficient...</td>
<td>... does increasing the dose</td>
<td>... compared to using the next medicine from the same/different drug group</td>
<td>... achieve better health outcomes?</td>
</tr>
</tbody>
</table>

Source: authors’ own compilation.
Table 6.2. Explanations to identify elements or items in the PICO framework

<table>
<thead>
<tr>
<th>Domain</th>
<th>Subdomain</th>
<th>Item(s)</th>
</tr>
</thead>
</table>
| Population                    | Disease and co-morbidities                     | Primary condition of interest  
                             |                                                                 | Secondary conditions of interest  
                             |                                                                 | (co-morbidities)                                                        |
| Non-modifiable                | Age                                            |                                                                         |
| person or population          | Gender                                         |                                                                         |
| characteristics               | Genetics                                       |                                                                         |
|                               | Ethnicity                                      |                                                                         |
| Modifiable                    | Anthropometric (weight)                        |                                                                         |
| person or population          | Type of community or organization              |                                                                         |
| characteristics               | Urban or rural                                 |                                                                         |
|                               | Exposure to toxins (may be a population-       |                                                                         |
|                               | defining factor that can be removed through    |                                                                         |
|                               | an intervention                               |                                                                         |
| Setting                       | Health-care system and provision               |                                                                         |
|                               | (tertiary/secondary/primary care)              |                                                                         |
|                               | Regulatory environment                         |                                                                         |
| Intervention                  | Type of intervention                           | Drugs/medication  
                             |                                                                 | Behaviour                                                                   |
| (may separate planned from    |                                                                 | Policy change  
                             |                                                                 | (Removal of toxins)                                                         |
| naturally occurring intervention or exposure) |                                                                 | Unintended effects of law-making  
                             |                                                                 | (Components of the intervention)                                           |
| Components of the intervention| What are the components?                      |                                                                         |
|                               | Who is administering or implementing the       |                                                                         |
|                               | intervention?                                  |                                                                         |
|                               | What is the intensity and duration of the      |                                                                         |
|                               | intervention?                                  |                                                                         |
| Naturally occurring           | Type of exposure                               |                                                                         |
| intervention                   |                                                |                                                                         |


| Comparator | No active comparison | Drugs: placebo  
Usual care  
Current policy continues to be used |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Active comparison</td>
<td>Same as intervention</td>
<td></td>
</tr>
</tbody>
</table>

**Outcome(s)**

- Health outcomes (beneficial and unbeneificial, including burden)

  - How is the outcome measured (valid)?
  - When is the outcome measured?
  - Is it a people- or patient-important outcome, or a surrogate outcome?

- Economic outcomes (resource use)

  - Resource units consumed

- System outcomes

  - Outcomes that measure impact on the health system

*Source:* considerations of the PICO elements, based on the work of Schünemann et al. (2013) (17).

### 6.4.3 Issues with health-care organization

Organizational questions are commonly addressed in guidelines and lend themselves to systematic reviews. The interventions are often complex; that is, consisting of multiple separate interventions that require joint consideration and may or may not depend on other components of the intervention. Examples include those listed here.

- Guideline question: should a multi-professional pain management team be established in a health-care institution to improve perioperative acute pain management?
- PICO question for systematic review or HTA: in acute-care hospitals, what is the impact of establishing a multi-professional pain management team on patient outcomes and on satisfaction of patients and staff?
- Guideline question: should a paediatrician, in addition to a family practitioner, be involved in management of all health problems in children?

Health-care questions address health outcomes but, in thinking about the scope, those proposing the guideline should also consider which of the other desirable and undesirable consequences in the EtD are relevant to the question.
6.4.4 Selecting and rating outcomes for health-care questions

When formulating questions to address health issues, the key outcomes that need to be considered should be identified. Typically, up to seven outcomes can be assigned to one question, but instead of being the result of the evidence, they must pertain to the relevant clinical or public health practice(s) for the patient, focusing on what is critical for decision-making and for creating recommendations. The outcomes should help to assess and measure the impact of comparative interventions used in the questions and they will also be used in examining and synthesizing the evidence. The more outcomes, the more literature will be used as a basis for the evidence. It is therefore important to focus on the outcomes that are significant to the patient, rather than choosing without critical judgement those that are easy to measure or often reported, unless they really are relevant. As such, it can be useful to have an early hearing of the important stakeholders (i.e. patients) regarding critical outcomes. Training material on the selection of outcomes is available on the McMaster University website (18). Outcome selection and rating involves three basic steps and should be carried out in GRADEpro (see Fig. 6.1).

Fig. 6.1. Identifying health-care questions and outcomes

Identifying and selecting outcomes for health questions involves three broad steps, as detailed here.

- Step 1 is to create an initial, comprehensive list of possibly relevant outcomes for each question, including both desirable health effects (such as reduced alcohol consumption, reduced viral load in people living with HIV, etc.) and undesirable ones (such as diagnostic delay, disease recurrence, complications, etc.) from the interventions that will be considered in the recommendations.
- Step 2 involves each member of the Panel evaluating the outcomes one by one
on a scale of 1–9, considering its importance to the patient (Fig. 6.2). The higher the value, the more critical the outcome. Rating an outcome in the range of 7–9 indicates that this outcome is very important or even critical for the patient and therefore also for making a decision to either recommend or not to recommend this intervention or diagnostic test. The range 4–6 indicates a significant indicator, and 1–3 is considered to be minor/negligible from the patient’s point of view. The same rating can be used several times (that is, the same number for more than one outcome). Given that people in different situations and from different backgrounds (patient, doctor, scientist, health official, etc.) can have very different opinions on the importance of the outcomes, the opinion of all the guideline developers matters.

**Fig. 6.2. Scale for the evaluation of outcomes**

<table>
<thead>
<tr>
<th>Scale:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- Of little importance
- Important, but not critical for decision-making (included in the table of evidence)
- Critical for decision-making (included in the table of evidence)

**Source:** GRADE handbook (2013) (11).

- Step 3 requires ratings to be tabulated by calculating the average score for each outcome. The results are submitted to the Panel, which decides which outcomes will be taken into consideration when assessing evidence and making recommendations. Generally, only important and critical outcomes are taken into account. GRADEpro can be used to facilitate direct identification, selection and rating of the importance of outcomes (see Fig. 6.1).
- If necessary, the final rating of outcomes can be reviewed and confirmed at this stage (e.g. at a Panel meeting).

### 6.5 Confirming and amending the scope

The final scope, approved by the Panel, together with the rated outcomes, are presented to the GAB for approval by the Chair of the Panel.

If it becomes evident during the guideline development process that the available evidence does not enable some of the questions to be answered as expected, or if the (unforeseen) need emerges to add topics, for the sake of completeness, it may be necessary to reword the question(s) or create (a) new question(s). This should be done alongside the submission of the interim report to the GAB (see Chapter 13).
7. Meetings and process considerations

The majority of the work involved in developing guidelines is carried out by the Guideline Secretariat, which searches for and synthesizes the evidence, and prepares preliminary answers to health questions along with guidance for formulating recommendations. The main task of the Guideline Panel is to assess the applicability of the collected evidence and its relevance to the situation in Estonia. On the basis of the evidence, the Panel formulates recommendations and determines their strength.

The Guideline Unit through the Secretariat supports the work of the Panel, arranges meetings, and provides methodological advice and support in the search for and synthesis of evidence-based scientific literature, the formulation of recommendations, and the writing of the guidelines. The Guideline Unit works with specific Panel members to progress the work on each EtD. The Guideline Unit should identify the requisite Panel members along with the Chair and the Secretariat.

7.1 Panel meetings

In order to ensure adequate cooperation in the development of the guidelines, the Panel will typically need to convene several times. Meetings may be conducted both in person and through electronic communication.

The purpose of the first meeting is to develop the questions, aiming to finalize the scope of the guideline. Once the GAB has approved the scope, the Panel reviews the evidence on the basis of the EtD frameworks prepared by the Secretariat and Guideline Unit for each recommendation. Recommendations are completed when the conclusion section of the EtD – which includes the implementation plan and indicators – is approved. The information in the EtD is presented to the Panel by the identified responsible Panel member or Guideline Unit member. This creates team spirit and a sense of ownership, and ensures topic relevance.

In addition, the meeting should be planned in detail and include:
- any DOI (at every meeting in case interests have changed);
- what the ground rules are for reaching a decision (at the first meeting and, if necessary, thereafter);
- what is expected from the meeting participants (at the first meeting and, if necessary, thereafter);
- what needs to be achieved during the meeting;
- what is to be done between meetings;
- what further activities are to be carried out by the Panel and the Secretariat.
The Panel meetings should be managed actively and in a constructive way, assisted by the instructions developed for the Chair of the Panel (see Annex 2). The meetings should not be used to question the methodology or the process (that can be done during an evaluation of the process). Indeed, it is assumed that with their consent to participate in the Panel, the members of the Panel undertake to comply with the principles and process specified in this handbook.

A Panel meeting has a quorum, if three quarters of the members are present. The tasks of a Panel member are not transferable and, if it becomes evident that such a member cannot participate permanently, a new Panel member should be appointed, if necessary.

The Chair should strive to make Panel decisions based on formal consensus. If no formal consensus can be reached, voting may take place (ideally anonymously, either in writing or using online voting tools). When the purpose of the meeting is to formulate recommendations, material must be prepared for the Panel at least 1–2 weeks before the meeting, including: a summary of the evidence detailed in the EtD tables (see Annex 4); and the draft recommendations.

If the recommendations have been discussed at the meeting and cannot be confirmed due to lack of quorum, the recommendations may be submitted for electronic voting, whereby all members of the Panel are asked to provide their judgments and opinions. 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, or other obvious flaws are detected.

Panel meetings should be recorded and include information such as the list of participants, agenda, activities, decisions, follow-up activities and any changes to any DOI of the Panel members. The completed and agreed upon EtD frameworks and judgements therein should be sent to all participants and are published on the website through a link from GRADEpro.

7.2 Secretariat meetings

The members of the Secretariat participate in the meetings of the Panel and submit the necessary materials to the Panel. As already mentioned, each Panel member has one or more specific questions assigned to them on which they work with the Secretariat. The Secretariat meetings can be conducted electronically, including by video conference (for example, via Skype), to save resources and time.
The collected evidence is discussed at the Secretariat meetings and the activities to be carried out are agreed during the periods between meetings. Such activities include:

- determining the availability of evidence on appropriate health questions from the selected credible guidelines, and developing and documenting a search strategy (and its results) for finding additional research evidence (e.g. systematic reviews or original studies) on questions that are not covered by the guidelines;
- reviewing and evaluating existing guidelines found, using the AGREE II tool (5), and selecting reliable guidelines for possible development (19);
- agreeing on which criteria of an EtD are critical for the guideline and preparing the EtD frameworks;
- drawing up a strategy for gathering (additional) evidence;
- producing a draft recommendation;
- obtaining or discussing feedback from the Chair of the Panel on summaries of the evidence and on the draft recommendation.
8. Evidence retrieval for guideline development

8.1 General considerations for prioritizing guideline development in Estonia

Guideline development in Estonia should be efficient, trustworthy and contextualized (2). To make the process efficient, existing guidelines and systematic reviews should be used as much as possible. A well-established process (20) is called adolopment, for the adoption, adaptation and de novo creation of guideline recommendations (19,21,22). A summary of all relevant research evidence is essential when developing a recommendation and, ideally, the summary should be based on systematic review(s). 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. Fig. 8.1 describes the general process of developing guidelines based on existing sources (19). Developing guidelines entirely de novo (that is, not basing them on existing guidelines) will be more resource- and time-consuming, but may be necessary for very specific topics.

8.1.1 Approach for efficient guideline development in Estonia

Translation of an existing guideline, however, is rarely sufficient (2). In order to ensure that the local context has been taken into account in developing the recommendations, the adolopment process should to be followed. One or more existing guidelines can be used as a basis for developing Estonian guidelines. These can be used as a model for formulating health questions, and where original/initial references to published evidence can be found. The Guideline Unit should establish contact with the original guideline developers; many are willing to share, or the information is already available publicly. For some organizations, asking for permission to use material (including paying fees) will be required, depending on the indicated copyright on the source material.

There are two primary objectives for adoption and adaptation of existing guidelines:
1. ensuring optimal and economical use of the existing human resources; and
2. making the guideline more user-friendly for the target audience, by assessing the factors characterizing local circumstances.
Fig. 8.1. The selection and process of using existing guidelines from other organizations

1. Selection of guideline topic and scope
2. Prioritization of question
3. Final identification of appropriate source guideline or systematic reviews
4. Matching of source guideline recommendations or systematic reviews to each prioritized question
5. Update systematic reviews as needed
6. De novo development

- Matching recommendation?
  - yes
    - ETD from source guideline?
      - no
        - Develop EtD
      - yes
        - Reassess ETD judgements
  - no
    - Adopted recommendation

- Adopted recommendation
- Adapted recommendation
- New recommendation

Adoption means using current recommendations in their unmodified form. Ideally, this means that the existing guidelines are reviewed and the decisions that led to their approval are agreed upon.

For the purpose of adoption, within the underlying guidelines there must be a clear, documented path to the recommendations; from the evaluation of the research to the preparation of the recommendation itself. If the path is deemed to be reliable, the Panel must assess the relevance and timeliness of the recommendations, with relevance here meaning that they are appropriate to the context of the Estonian health-care system. In order to confirm the timeliness, if a few years have passed since the preparation of an international guideline, it may be necessary to re-examine the scientific evidence, to make sure that any new essential material has been added.

Adaptation means that reliable guidelines have been found that meet the established criteria, but the recommendations are not directly suitable for use in the Estonian cultural or organizational context; they do not precisely answer the health questions contained in the Estonian guidelines; or they need to be updated based on newly available evidence.

Adoption and adaptation are combined into the methodology called adolopment, developed for using adoption, adaptation and de novo creation of guidelines, alongside and in accordance with the GRADE methodology (see Fig. 8.2).

From time to time, where guideline recommendations are required, no direct evidence will be available to answer some of the health questions. In such cases the Panel must document the reasoning and justification for compiling the recommendation (in EtD format), based on indirect evidence (see Fig. 8.3). Such a recommendation may then also become the basis for a proposal for further research.

Guidelines in Estonia will therefore be established based on:
- recommendations developed from published health guidelines that were created by independent national and international authorities (e.g. the National Institute for Health and Clinical Excellence (NICE), WHO, and other international professional organizations that follow evidence-based approaches to guideline development) and that meet specified criteria;
- recommendations developed from published clinical guidelines that were created by specialty societies that are not commercially funded, and that follow standardized criteria for guidelines (e.g. that provide evidence summaries and adequate descriptions of the processes used to manage any COI);
- recommendations developed from existing systematic reviews.
1. Identify and prioritize credible existing guidelines or evidence syntheses of interest and relevance

2. Evaluate and complete GRADE EtD framework for each recommendation

1. GUIDELINE TOPICS
   - Identify topics, e.g. by priority setting and identifying existing guidelines or evidence syntheses with appropriate stakeholders
   - Involve stakeholders to agree that guideline questions are relevant and will yield useful and trustworthy recommendations

2. EtD CRITERIA
   2.1 Check for transparent description of criteria that determine the direction and strength of individual recommendations, including evidence and judgements influencing recommendations (ideally a complete EtD framework is available)
   2.2 Begin completing or utilizing an existing GRADE EtD framework

3. GRADE-ADOLOPMENT of recommendations in a guideline (adoption, adaptation, and de novo)
   - Use relevant information but complete EtD framework obtaining research evidence or additional considerations for new recommendation

**Fig. 8.3. Establishing whether the recommendation is adopted, adapted or new**

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>ORIGINAL</th>
<th>IMPORTANCE FOR DECISION</th>
<th>ADOLPMENT</th>
<th>IMPORTANCE FOR DECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROBLEM</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>LOW</td>
</tr>
<tr>
<td>DESIRABLE EFFECTS</td>
<td>Large</td>
<td></td>
<td>Large</td>
<td>HIGH</td>
</tr>
<tr>
<td>UNDESIRABLE EFFECTS</td>
<td>Moderate</td>
<td></td>
<td>Large</td>
<td>HIGH</td>
</tr>
<tr>
<td>CERTAINTY OF EVIDENCE</td>
<td>Very low</td>
<td></td>
<td>Very low</td>
<td>HIGH</td>
</tr>
<tr>
<td>VALUES</td>
<td>Important uncertainty or variability</td>
<td></td>
<td>No important uncertainty or variability</td>
<td>HIGH</td>
</tr>
<tr>
<td>BALANCE OF EFFECTS</td>
<td>Probably favors the intervention</td>
<td></td>
<td>Probably favors the intervention</td>
<td>HIGH</td>
</tr>
<tr>
<td>RESOURCES REQUIRED</td>
<td>Varies</td>
<td></td>
<td>Moderate savings</td>
<td>MODERATE</td>
</tr>
<tr>
<td>CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES</td>
<td>Very low</td>
<td></td>
<td>Very low</td>
<td>LOW</td>
</tr>
<tr>
<td>COST EFFECTIVENESS</td>
<td>Varies</td>
<td></td>
<td>Probably favors the intervention</td>
<td>MODERATE</td>
</tr>
<tr>
<td>EQUITY</td>
<td></td>
<td></td>
<td>Probably increased</td>
<td>HIGH</td>
</tr>
<tr>
<td>ACCEPTABILITY</td>
<td>Probably yes</td>
<td></td>
<td>Yes</td>
<td>HIGH</td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>Probably yes</td>
<td></td>
<td>Yes</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

*Source: Schünemann et al. (2017) (19).*
All guidelines that are used as sources should be assessed in terms of their quality using the AGREE II tool. For example, they all should include systematic reviews. Many guideline-producing organizations rely on groups such as the Cochrane Collaboration to identify 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 to only occasionally develop de novo recommendations. This is based on the assumption that research evidence to support a particular recommendation is usually global, whereas costs, values and preferences, and the equity, acceptability and feasibility of recommendations are local considerations, and therefore should form the basis of adaptation of international recommendations.

Systematic reviews can be assessed for quality using the latest version of the ROBIS checklist. When developing recommendations, the Panel compares its judgements to those of the original Guideline Panel and determines if any changes to recommendations are required (see Fig. 8.4).

8.2 Retrieving and assessing existing guidelines

It is strongly recommended that the search for evidence be carried out in consultation with an expert in information retrieval (e.g. a librarian, or medical research assistant) to ensure a sound search strategy is used. As described earlier, the process starts 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 PubMed, should be searched (Annex 10):

- National Guideline Clearinghouse http://www.guideline.gov/
- the GIN database http://www.g-i-n.net/library
- the GRADE Working Group database http://dbep.graepro.org/
- websites of specialist medical societies relevant to the topic and the scope of the proposed guidelines.
- Websites of guideline-producing agencies can also be searched, including:
  - 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
Fig. 8.4. Making judgements by adopting recommendations

A sample search strategy for the initial search is provided in Annex 11. It should include the National Library of Medicine (NLM)’s 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.⁹

If several potentially relevant guidelines are identified through the initial search, the Panel should 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. It is useful to prioritize sources that have GRADE EtD frameworks, or substantive references to systematic overviews.

The search strategy used should be documented and should specify:
- the details of the databases (including websites) 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 guidelines. Potentially relevant citations should be retrieved as abstracts, if possible, and then further screening should be undertaken to identify possible guideline documents. These should then be retrieved in full text.

Relevant guidelines should then be assessed for the following aspects.
1. Are the guidelines based on explicit use of evidence?
   - If not, they should not be used.
   - If they are evidence based, are evidence summaries provided? (E.g. GRADE summary of findings tables (SoF tables) and evidence profiles, or references to systematic reviews.)

2. Who funded the guideline development?
   - If the funding was from commercial sources, what processes were used to manage any COI? If these are not described, the source of funding has not been disclosed, or no measures to control any potential COI have been implemented, the guidelines should be excluded. However, there may be relevant systematic reviews or evidence profiles incorporated into them that may be helpful.

⁹ MeSH is the NLM controlled-vocabulary thesaurus used for indexing articles for PubMed (http://www.ncbi.nlm.nih.gov/mesh).
A summary of the publications assessed, and reasons for the exclusion of any of them, should be prepared by the Secretariat for review by the Panel at the first meeting to ensure that any exclusion of publications is appropriate.

3. What is the credibility of the guideline, based on the AGREE II rating instrument?

The key questions in the AGREE II instrument relevant to the quality of a guideline for subsequent consideration are numbered 8–11 and 22–23 (see Box 8.1). 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 person rating them, the guideline is probably too poor in quality to be useful.

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 summarized. The process involves deciding to accept or modify whole guidelines or their specific recommendations by considering whether they are credible, up to date, acceptable and applicable, given the cultural and organizational context. The next critical step after identifying potentially matching recommendations includes completing or using GRADE EtD frameworks for recommendations for either a matched recommendation or a new recommendation. This often requires conducting updates of existing systematic reviews. It may require major and minor updates, or defining a new systematic review (19, 23). Depending on agreement with the information presented in the existing guidelines or requirements for new evidence, recommendations are adopted or adapted. If no information or recommendation is available, a new recommendation is developed. That is, if the recommendations and the sources of evidence are the same, the main considerations in deciding to adopt the recommendations locally will be based on factors of cost, values and preferences, equity and feasibility.

If there are very few guidelines (just one or two) that make recommendations for a particular question, it will probably be necessary to review the references (systematic reviews and randomized controlled 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 Guideline 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.

**Box 8.1. AGREE II instrument questions 7–11 and 22–23**

Q7: Systematic methods were used to search for evidence.
(7 Strongly agree … 1 Strongly disagree)

Q8: The criteria for selecting the evidence are clearly described.
(7 Strongly agree … 1 Strongly disagree)

Q9: The strengths and limitations of the body of evidence are clearly described.
(7 Strongly agree … 1 Strongly disagree)

Q10: The methods used for formulating the recommendations are clearly described.
(7 Strongly agree … 1 Strongly disagree)

Q11: The health benefits, side-effects and risks have been considered in formulating the recommendations.
(7 Strongly agree … 1 Strongly disagree)

Q22: The views of the funding body have not influenced the content of the guideline.
(7 Strongly agree … 1 Strongly disagree)

Q23: Competing interests of guideline development group members have been recorded and addressed.
(7 Strongly agree … 1 Strongly disagree)

*Source: AGREE Next Steps Consortium (5); Brouwers et al. (24).*

If the guideline has used GRADE profiles or SoF tables as the basis for evidence presentation, it may be possible to update the evidence profile and then reassess the recommendation with regard to the health benefits and harms related to an option, adding in considerations of costs, local values and preferences, and feasibility. If the recommendations in the guidelines that are used differ from each other, it is likely that further evidence retrieval will be needed. If there are no usable existing guidelines or recommendations for a particular question, it will be necessary to retrieve existing systematic reviews (see subsection 8.3).

8.3 Retrieving and assessing systematic reviews and meta-analyses

8.3.1 Retrieving existing systematic reviews

8.3.1.1 Importance of systematic reviews

High-quality systematic reviews reduce the risk of selective citation and improve the reliability and accuracy of decisions. If systematic reviews are to be used in
guideline development, they should be assessed for how well they have been carried out; that is, how credible they are.

The key features of a trustworthy 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 synthesizing the results and, if feasible, a quantitative synthesis of the results of studies to estimate the overall effect of an intervention (meta-analysis).

8.3.1.2 Finding systematic reviews

The first step is to identify relevant systematic reviews for each of the questions, using PubMed and related databases. 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. This includes searches of the Cochrane Database of Systematic Reviews (Annex 10).

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 irrelevant citations 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.

8.3.1.3 Assessing the credibility of systematic reviews

Once the reviews are retrieved, they should be checked for:
- potential commercial sources of funding – any reviews funded by pharmaceutical companies should be excluded unless there is no alternative review on the same topic;
- 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 should be assessed by using the most recent version of the ROBIS instrument, as a critical appraisal instrument (see Annex 12). Ideally, this should be carried out by two members of the Secretariat and results compared.

Based on the ROBIS instrument assessment results, reviews may be excluded
from further use if both people rating them agree that there were no pre-speci-
fied criteria for including studies and there are concerns about the declaration of a COI. Otherwise, the reviews should be included. If there are several relevant systematic reviews, the most recent one that is of high quality should be used. If the review is of high quality, but more than two years old, updating the review should be considered 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.

The Secretariat then prepares SoF tables, which include:
- the recommendations from the included guidelines;
- results relevant to each question and outcome from the guidelines and systematic reviews, to present to the Panel.

Annex 13 provides a table template for summary tables of guideline recommendations. For summary tables of results from systematic reviews for each question and its outcomes, GRADE SoF tables and EtD frameworks should be used (25,26) or, if all else fails, study-by-study tables, using the template in Annex 14. The SoF tables will need to be supplemented with short narratives that describe the nature of the evidence. An example of such 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 randomized controlled trials (21 567 subjects) that compare treatment A with treatment B.”
9. Evidence preparation and certainty of evidence

Assessing the evidence retrieved is a crucial step that enables the Panel to formulate recommendations. The GRADE approach (9) is used by over 100 organizations, including WHO, the European Commission and NICE. The approach is used for preparing evidence profiles and GRADE SoF tables, as well as developing recommendations and making decisions, which includes assessing the certainty of evidence. GRADE also uses the terms “quality in the evidence” or “confidence in the effect estimates” as alternative expressions for certainty of evidence.

GRADE is also used for developing recommendations by using GRADE EtD frameworks (see Annex 4). 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 desirable and undesirable health outcomes (benefits and harms) that have been rated as important, supplemented by evidence about other criteria in the EtD. EtDs can be used to adopt, adapt or develop de novo recommendations (see subsection 8.1.1 on adolopment).

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

The GRADE handbook (11), available at the GRADEpro website10 includes the instructions for developing GRADE evidence profiles and for assessing the quality of evidence and developing recommendations. Alongside all other aspects of the EtD and guideline production, it includes an adolopment module. A brief overview of the GRADE approach is provided in the subsections that follow.

10 https://gradepro.org/
9.1 Using GRADE

The GRADE approach has two main steps: (i) evaluation of the certainty or quality of evidence and the preparation of GRADE SoF tables, and (ii) developing recommendations, for example by using the GRADE EtDs.

9.1.1 Evaluation of the certainty or quality of evidence

Certainty in the evidence is defined as the extent to which one can be confident that an estimate of effect or association is correct or crosses a certainty threshold. It is a continuum; any discrete categorization involves some degree of arbitrariness. It is based on the signalling questions (followed by GRADE term and explanation), listed here.

- Are the research studies well done? Consider any limitations in study design and execution or risk of bias.
- Are the results consistent across studies? Is there any inconsistency across the available studies when there should be none?
- How directly do the results relate to our question? Observe any indirectness (transferability, applicability, generalizability or external validity) of the evidence with respect to the populations, interventions, and settings where the proposed intervention may be used.
- Is the effect size precise – due to random error? Is there any imprecision based on wide or narrow confidence intervals (CI) and other considerations?
- Are these all of the studies that have been conducted? Consider publication bias.
- Is there anything else that makes the team particularly certain, primarily when there are observational studies of effects? Take into account large effects, worst-case scenario predictors (even these can still result in strong conclusions), and the exposure–effect relation.

Certainty of evidence is categorized as high, moderate, low or very low and the definitions are shown in Table 9.1.

The assessment of quality of evidence is supported by GRADEpro software. The domains for the rating process are summarized in Table 9.2.
Table 9.1. Categories of certainty of evidence and their definitions

<table>
<thead>
<tr>
<th>Ratings</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>⬤⬤⬤⬤ High certainty</td>
<td>The Panel is very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>⬤⬤⬤ Moderate certainty</td>
<td>The Panel is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>⬤⬤ Low certainty</td>
<td>The Panel’s confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>⬤ Moderate certainty</td>
<td>The Panel has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.</td>
</tr>
</tbody>
</table>


Table 9.2. GRADE certainty of evidence assessment domains

1. Establish initial level of certainty

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial certainty in an estimate of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>High certainty</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low certainty</td>
</tr>
</tbody>
</table>

2. Consider lowering or raising level of certainty

<table>
<thead>
<tr>
<th>Reasons for considering lowering or raising certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower if</td>
</tr>
<tr>
<td>Higher if*</td>
</tr>
</tbody>
</table>

3. Final level of certainty rating

<table>
<thead>
<tr>
<th>Certainty in an estimate of effect across those considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Very low</td>
</tr>
</tbody>
</table>

*Upgrading domains is usually applicable to observational studies only.


9.1.2 Preparation of a summary of findings

A summary of findings should be prepared, showing the results of the systematic review (and studies), using both relative and absolute measures. SoF tables (see Annex 15 and Annex 16) for GRADE evidence profiles are constructed using 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, either use an existing one from another guideline or identify the systematic review(s) that include studies reporting the relevant outcomes. Not all studies in the reviews may report the outcome of interest and not all outcomes of interest are measured in studies. For each outcome, data should be presented from the subset of studies in the review that reported it, and it should be indicated if no study reported or measured it.

The column “number of studies” should be filled in, indicating the number of studies in the review that report the outcome. For future reference and checking, it is suggested that these studies are listed as a footnote to the table.

The certainty of evidence assessment should be carried out for these studies using 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 of people with an 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% CIs.

It is advisable that one reviewer extracts data from the systematic reviews and/or from single studies and prepares drafts of the GRADE tables with detailed footnotes explaining the judgements that were made. This is explained in detail in GRADEpro and in the updated chapters of the Cochrane Handbook for Systematic Reviews of Interventions (27). Each judgement 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. Interactive versions of SoF tables can be useful for presenting information to guideline panels or to a lay audience.11

11 See, for example, a presentation of information used as the basis for a 2019 systematic review and meta-analysis, published in The Lancet (28).
9.1.3 GRADE EtD frameworks

The aim of EtD frameworks is to help panels use evidence in a structured and transparent way to inform decisions in the context of health recommendations, coverage decisions, and health system or public health recommendations and decisions (25, 26, 29–31). The frameworks have a common structure that includes formulation of the question, an assessment of the evidence, and drawing conclusions, although there are some differences between frameworks for each type of decision. They can be adapted to the context and interactive versions are available through GRADEpro. EtD frameworks provide a systematic and transparent approach for moving from evidence to health-care decisions. EtD frameworks inform Panel members and users of the recommendations about the judgements that were made and the evidence supporting those judgements, by making the basis for decisions transparent to target audiences. EtDs also facilitate dissemination of recommendations and enable decision-makers.

9.2 Assessing cost and resource implications, equity, acceptability and feasibility

In addition to the 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. Therefore, costs and resource use are one of the criteria embedded in the EtD. The Panel must also consider the capacity of the existing health system and the feasibility of implementing the recommendations. This implies assessing the need for additional resources, the need for and availability of the labour force, as well as preventive and diagnostic interventions and administrative costs. It is important to note in the EtD whether research evidence was sought, or if it is a judgement of the Panel based on evidence provided (32).

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

After defining the final scope of the guideline, the Panel has to decide which health questions are most likely to require consideration of costs and resource use in detail, including those for which a formal economic evaluation – as well as the budget impact analysis – may be required. If the guideline deals with options or interventions that are not yet listed in the official list of health-care services or
reimbursed medicines financed in Estonia, consideration should be given to submitting corresponding applications in accordance with the procedure established by legislation.

The Secretariat provides an overview of the expected budget impact of the initial recommendations, compared to current or comparative practices. This analysis consists of three steps:
1. identifying what type of resource use is associated with the recommendation;
2. measuring how much of this is used;
3. determining the monetary value (that is, how much it costs).

A description of resource use and costs should be prepared from the point of view of the health-care system, describing the main resources needed to implement the recommendations. It is important to include resource use associated with the provision of the intervention, subsequent investigations and care, and adverse effects. In addition to the health insurance budget, the costs of other stakeholders should be taken into account (e.g. cost-sharing by patients, state budget impact, and so on).

In order to respond to questions affecting resource use, it is advisable first to identify relevant existing budget impact and cost–effectiveness analyses. If a significant change in treatment practices in Estonia is implicated, it may be necessary to carry out a focused budget impact analysis in cooperation with the EHIF, using its databases of health-care service claims and reimbursed pharmaceuticals. After evaluating the effectiveness of the intervention, the economic feasibility and affordability of the recommendation should also be assessed.

9.3 Presenting the evidence to the Panel

As described earlier, the goal of the EtD framework is to help the Panel to use the evidence in a structured and transparent way, to allow informed decisions to be made about the guideline recommendations and their effects. The structure of the framework includes formulating questions, assessing evidence, and drawing conclusions leading to final recommendations.

The structure of the EtD summary can be adapted to the context, and interactive versions are available in GRADEpro. Both the members of the Panel and the users of recommendations can see from the EtD summary the evidence on which decisions were made in the preparing the recommendation, which ensures the decision-making process and judgements are transparent. EtD summaries also facilitate the implementation of recommendations and evidence-based decision-making.
At least one week before the meeting, the Panel should receive an initial GRADE EtD for each question, containing the GRADE evidence profile tables with a preliminary assessment of the impact of the recommendation on resources, applicability, values, equity, as well as feasibility and acceptability.

The members of the Panel should assess whether the EtD summary lacks any significant aspect that is necessary for the formulation of the recommendation, before the meeting. This should be in collaboration with the member of the Panel assigned to the question, who will either present the information to the Panel or support the presentation. The summaries completed by the Panel are used to formulate recommendations and determine their strength.
10. Development of recommendations

The guideline recommendations are formulated by the Guideline Panel on the basis of an EtD and the draft recommendation provided by the Guideline Secretariat, which prepared the question(s). It is important to note that the draft functions as a starting point, but should not dictate the recommendation that is made.

Recommendations must enable a clear view of the user (society, health-care system or patient) and what outcomes and criteria were considered when making them. The recommendations should be clearly and precisely worded and describe the action unambiguously (e.g. “use treatment A for all patients with disease B”).

For all recommendations, the direction of the recommendation (for/against), its strength (strong/conditional), and a summary of the quality of the evidence used to formulate it (high/moderate/low/very low) should be determined. The evidence in the EtD summary should be used in developing recommendations. The recommendation for each health question takes into account: the evidence relating to the question and its quality; the possible harm–benefit ratio; the values and preferences of patients; the applicability of the activities related to the recommendation; and equality of access to the service.

To explain the answer to each health question, the Secretariat prepares explanatory summaries within an EtD table, explaining the background of the recommendation. This includes:
- important results found in the guidelines, systematic reviews and meta-analyses;
- evidence gathered using a systematic research approach;
- criteria taken into account in addition to the evidence.

During the development of a recommendation, it may appear that in order to respond to a single health question, more than one recommendation should be formulated, appropriate to different situations or groups of users.

If no evidence exists in order to draw up a recommendation on a health-related question, the Panel must document, in the EtD format, the judgements established for the recommendation, justifying the decision made.

10.1 From evidence to recommendations

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

- The question should be clearly introduced.
- 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 from among the Secretariat, including resource and use costs, budget impact (as well as possibly cost–effectiveness), along with values and preferences.
- The draft recommendations are presented by the Secretariat, with justification and reference to the relevant evidence in the GRADE EtDs.
- If necessary, the first recommendation is modified.
- Final agreement on the recommendation is reached.

In the context of the EtD framework, consensus is defined as general agreement by the non-conflicted panellists about a criterion or a recommendation. Consensus is typically achieved through group discussion and compromise, which is facilitated by the Panel co-Chair(s). Operationally, consensus is reached when no voting member of the Panel requests changes or further discussion on a criterion or a recommendation. For example, when a minority disagrees with a majority, discussion often can identify modifications that allow the minority to agree with the recommendation (which sometimes can be just a minor modification, for example relating to dosing/administration).

With the use of EtDs, panels typically reach consensus about criteria or recommendations without formal voting. Voting may cut short discussion before consensus is achieved, resulting in a judgement or recommendation that has weaker group support than a decision reached through continued discussion. However, if necessary (in situations where no consensus is reached, members request voting, or if discussion is too lengthy about the judgement on a criterion), voting can be used as a method of last resort to force a decision.

10.1.1 Approach to achieving consensus

The process is guided by the Panel co-Chair(s). This can be done either online or in person.

For judgements about EtD criteria, the Panel uses the stepwise approach outlined here.

- The process should be carried out on a per-recommendation basis; that is, all judgements are made for each recommendation.
- Judgements should be requested on each criterion, first suggested by one Panel member (unless the answer is already clear: for example, often the process of prioritization highlights whether the problem is a priority or not); or, if similar questions have been answered for other recommendations, the Chair may suggest the respective judgement or answer.
- If it becomes clear that one or a few members of the panel are too opinionated or influential, the Chair will ask other Panel members for their initial judgement first.
- Participants should be explicitly requested to express any disagreement.
- If no consensus is reached after discussion, the Panel may resort to voting.
  • Simple majority rules should be implemented (e.g. about the benefits, harms, resource use).
- If any individual or a few members disagree, the Panel Chair can ask if the Panel members wish to note this in the additional consideration column (either mentioning the Panel member’s name, or without assigning a name to the comment).

For agreement on the final recommendations (conclusion section), the following process should be followed.

- The Panel co-Chair(s) will ask for a suggestion by one member (or will make a suggestion).
- They will ask for any disagreement to be expressed.
- Some suggestions may be made by the co-Chair(s). For example:
  • if direction is clear, they may start by suggesting that the summary of judgements indicates that the recommendation is in favour or against, but that the strength needs to be determined.
- If required, the Panel Chair(s) will revert to a vote and note the results of voting (in person, but using anonymous recording methods).
- The focus should first be on the direction of the recommendation (decided by simple majority), and then on its strength (an 80% majority is required for a strong recommendation).
- The five paradigmatic situations that have been defined for strong recommendations, in the face of low- or very low-quality evidence, must apply to strong recommendations in that context (see Annex 17).

10.2 Involvement of Panel members with and without COI

All members will be involved in:
- preparing and reviewing research evidence;
- important additional considerations during the review of the research evidence;
- all stages up to the final step of making judgements and decisions on strength and direction of the recommendation (these are only to be made by non-conflicted members);
- meetings in person (conflicted members will be asked to remain silent and speak only when asked);
- the end of the process, at which point discussion is open to all.

Changes to the conclusions are unlikely (only if obvious errors were made that would change them).
Only non-conflicted members will be involved in:
- judgements on criteria;
  • (when online) only these members will be invited to make judgements;
- agreement on conclusions and recommendations.

Managing this process requires good chairing (the checklist for Panel Chair(s) should be used; and a checklist for Panel members is being prepared), including clarifying and adhering to the rules in this handbook. However, experience shows that this does not tend to be a problem.

**10.3 Grading the strength of recommendations**

The strength of the recommendation reflects the degree of confidence that the desirable consequences of adherence to the recommendation outweigh the undesirable effects. Desirable consequences can be, for example, beneficial health outcomes, less burden, and greater savings. Undesirable consequences include, for example, harms and increased costs. Burden here refers to the demands of adhering to a recommendation that patients or caregivers (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 approach defines two categories of recommendation: strong and conditional (also known as weak) (see Box 10.1). 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 consequences of adherence probably outweigh the undesirable consequences, but the group is not confident about the trade-off.

Reasons for not being confident may include:
- absence of high- or moderate-quality evidence;
- presence of imprecise estimates of benefit or harm;
- uncertainty or variation in how different individuals value the outcomes;
- small (health) benefits;
- benefits that are not worth the costs (including the costs of implementing the recommendation).

However, there are five paradigmatic situations that allow a strong recommendation to be given, even in the absence of high or moderate certainty of evidence (Annex 17).

The Panel must consider all known factors and justify the reasons for its decisions in detail, in order to maintain the recommendation’s credibility. A definite recommendation is only made if the intervention or medicine meets the (capacity) requirements of the Estonian health-care system.
Box 10.1. Interpretation of strong and conditional recommendations

Interpretation of a strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy-makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgements that mean that additional research is unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of evidence. In such instances, further research may provide important information that alters the recommendation.

Interpretation of a weak or conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient’s values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy-makers: policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgements, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help to identify possible research gaps.
The formulation of recommendations is a very important step in the preparation of guidelines. As the users of the guidelines can only consult recommendations, these should be concise, clear and practicable. Each recommendation – or the wording of the recommendation, provided as a bullet-point list – must contain only one primary activity. The recommendations should use the same style and terminology throughout and should take into account the linguistic and cultural context in which readers will understand them (see Table 10.1 for an example). Formulation of recommendations should be based on the approach outlined here.

- The focus should be on what to do or what to use.
- Simple language should be used (in Estonian), avoiding ambiguity.
- Only the information necessary for the reader should be used.
- The strength of the recommendation should be included in the wording (in parenthesis following the recommendation, together with the certainty of evidence).
- The words person or patient should be used instead of the words individual, case, or subject. If possible, it is preferable to use the word person, rather than the word patient for people with mental health problems or long-term illnesses. In the case of people with mental health problems, the term service recipient may also be used, instead of the word patient. The word patient should not be used for people who do not have a disease or condition (e.g. a pregnant healthy woman).

Table 10.1. Wording of recommendations

<table>
<thead>
<tr>
<th>Strong recommendation for</th>
<th>Wording 1</th>
<th>Wording 2</th>
<th>Wording 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation for</td>
<td>We recommend…</td>
<td>Clinicians should…</td>
<td>We recommend…</td>
</tr>
<tr>
<td>Weak recommendation for</td>
<td>We suggest…</td>
<td>Clinicians might…</td>
<td>We conditionally recommend…</td>
</tr>
<tr>
<td>Weak recommendation against</td>
<td>We suggest…not</td>
<td>Clinicians might not…</td>
<td>We conditionally recommend…not</td>
</tr>
<tr>
<td>Strong recommendation against</td>
<td>We recommend …not</td>
<td>Clinicians should not…</td>
<td>We recommend …not</td>
</tr>
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</table>

Annex 18 gives some examples of wording in Estonian for various recommendation scenarios.
10.4 Good practice statements

Good practice statements represent recommendations that guideline panels feel are important but that are not appropriate for formal ratings of quality of evidence. These statements characteristically represent situations in which a large and compelling body of indirect evidence – made up of linked evidence, including several indirect comparisons – strongly supports the net benefit of the recommended action. Linked evidence means that several separate bodies of evidence together allow inferences regarding net benefit (e.g. evidence regarding diagnostic test accuracy (DTA) and evidence regarding the effectiveness of treatment implemented on the basis of that test). To issue a good practice statement, the Panel should ensure five key criteria are met (see Box 10.2).

**Box 10.2. Conditions to be met for good practice statements**

A question applicable to any recommendation is:

(i) is the statement clear and actionable?

Questions particular to good practice statements include those listed here (ii–v).

(ii) Is the message really necessary in regard to actual health-care practice?

(iii) After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences?

(iv) Is collecting and summarizing the evidence a poor use of a Guideline Panel’s limited time and energy (e.g. opportunity cost is large)?

(v) Is there a well-documented clear and explicit rationale connecting the indirect evidence?

*The answers to all questions (ii) to (v) should be yes in order to proceed with a good practice statement.*

10.4.1 Examples of acceptable good practice statements\(^\text{12}\)

- For patients with congenital adrenal hyperplasia, it is recommended to monitor patients for signs of glucocorticoid excess (ungraded good practice statement).

\(^{12}\) Note that ungraded good practice statements are denoted as such, following the statement, as these examples show.
- Health services should be made available, accessible, and acceptable to sex workers based on the principles of avoidance of stigma, non-discrimination, and the right to health (ungraded good practice statement).
- Patients with chronic pain not related to cancer that are considering opioid therapy should be made aware of non-opioid alternatives (good practice statement).
- In patients presenting with heart failure, initial assessment should be made of the patient’s ability to perform routine/desired activities of daily living (ungraded good practice statement).
- The Panel believes that in patients presenting with heart failure, initial assessment of the patient’s ability to perform routine/desired activities of daily living represents good practice (ungraded good practice statement).
- In patients presenting with heart failure, clinicians should make an initial assessment of the patient’s ability to perform routine/desired activities of daily living (ungraded good practice statement).
11. Interim report, review, and approval of guidelines

Guidelines should be developed in accordance with the principles and methodology set out in this handbook, and the evidence-based nature and clarity of the recommendations should be guaranteed. Any methodological and substantive issues emerging during guideline development are to be addressed by the Guideline Unit.

11.1 Interim report

In order to monitor the compliance of the guideline development process with the approved scope and timetable, the Panel submits an interim report on the development of the guideline to the GAB, no later than six months after the approval of the scope. The interim report should describe the progress on the formulation of evidence-based recommendations and, if necessary, make reasoned proposals for modifying or complementing clinical issues in the final scope.

If necessary, the Chair of the Panel will submit suggestions for changes in the composition of the Panel and/or the Secretariat; for example, if an additional expert needs to be involved.

11.2 Review

When the guideline is close to being finalized, the GAB initiates a review by three reviewers (ideally a general practitioner, a content expert and one GAB member). The Chair of the Panel submits the final draft (approved by the Panel) to the Guideline Unit, who forwards it to the approved reviewers, as well as for consultation by other relevant parties.

A Panel member reviews the received feedback and comments, together with the Guideline Unit, and suggests any required changes to the guideline to be made by the Secretariat. Substantive changes will have to be approved by the Panel based on recommendation by the the Chair; justifications for any amendments should be provided.

11.3 Approval by the GAB

In order for the GAB to approve the guideline, including its implementation plan and other relevant material, it has to evaluate whether the guideline has been developed according to the principles and methodology set out in this handbook, and whether the necessary processes have been followed and documented (see Fig. 11.1).
The focus of the evaluation and subsequent discussion in the GAB is not the content of the guideline, but the rigor of its development. In general, this evaluation should follow the principles highlighted in the GIN-McMaster checklist, developed in collaboration with Estonia (8), as well as the AGREE II tool (5), and the checklist accompanying the Essential Reporting Items for Practice Guidelines in Healthcare (RIGHT) statement (33,34).

The key questions that would signal to the GAB the quality, clarity and consistency of a guideline include those listed here.

- Did the Panel and the Secretariat report using the RIGHT (and, if an adaptation, RIGHT ADAPT) reporting checklist(s)?
- Did the recommendations appropriately describe the population, intervention and comparator (if necessary) and include the rating of the strength and quality/certainty of the evidence?
- Is there a link between the evidence and the recommendations?
- Are the reasons for the EtD judgements clear?
- Did the guideline working group only make strong recommendations when justified? (The rationale for all strong recommendations should be checked.)
- Was COI appropriately managed and addressed? (The meeting minutes should be checked.)
- Are the results of the public consultation available?
- How does the guideline score on the AGREE items?

Fig. 11.1. The process of review and approval

Source: authors’ own compilation.
12. Dissemination of the guideline recommendations

The reliability of guidelines is ensured by maximum transparency of the development process. To enable this, the procedure for preparing the guideline must be carefully documented and all documents involved should be stored electronically in order to be publicly disclosed and used again in future.

All topic proposals and scopes approved by the GAB, along with the minutes of the meetings of the GAB are publicly available on the website.13 Recommendations that have been completed and approved by the Panel during the guideline development process are also published (in SIRU format) on the guidelines’ website.

During the guideline development process, implementation plans are prepared for the dissemination and use of the information contained in the guidelines by the various target groups. The evaluation metrics for implementing the guidelines are also provided.

Once the guideline development process reaches the final stage, all assessments, comments, and reviews of interested parties are made publicly available, in addition to the working copy of the guideline, the summaries of the evidence gathered by the team, the protocols of the Panel meetings, and an overview of any DOI.

Following approval of the guideline, the following items are also made available on the website:
- recommendations (in SIRUs);
- the guideline in full (in web and printable (.PDF) versions);
- algorithm(s) illustrating the choices and recommendations given in the guideline (if created) (in web and printable (.PDF) versions);
- a short version (executive summary) of the guideline if necessary (1–2 pages);
- patient recommendations and patients versions (if applicable) (in web and printable (.PDF) versions);
- the implementation plan;
- the final scope of the guideline;
- summaries of the evidence/findings and EtD summaries;
- minutes of the Panel meetings;
- an overview of any DOI of the guideline developers, listing their names and professions.

Depending on the guideline topic the information from the recommendations, EtD summaries and algorithms is integrated into a clinical decision support tool, which is developed and maintained by the EHIF.

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12.1 Guidance material based on the guideline

12.1.1 Algorithms and other instructional materials

In order to illustrate the choices and recommendations offered in the guidelines, it is often useful to develop algorithms describing the treatment of patients and reflecting the movement of patients through the Estonian health-care system.

In this handbook, the term algorithm (clinical pathway) means consolidated information or a step-by-step guide, presented as a schematic diagram (e.g. as a flowchart of the process), including activities for a specific target group of patients within a defined time period. The algorithm is based in part on substantial evidence that links various health-care professionals to the process of joint decision-making, while also reflecting the structure of the Estonian health-care system by facilitating the division of labour to provide the patient with appropriate services.

The algorithm outlines the purpose and main elements of the activities (research, treatment, etc.), taking into account ethical practice, patient expectations, the national health-care system and the necessary sequence of activities. In addition to the mapping of patient mobility in different treatment stages, patient-related information is documented and movement between different health-care providers is also described.

The algorithm is developed by the Secretariat, which submits it to the Panel for supplementation and agreement. In the near future, GRADEpro will allow these pathways or algorithms to be developed within the tool. The algorithm is based on the guideline recommendations, informed by scientific sources and the organization of the Estonian health-care system. If the algorithm presents different solutions compared to the current division of labour (in terms of the sequence of the provision of health services or the assignment of tasks) the Panel must justify the feasibility of and approach to the evidence underpinning the proposed changes. The algorithm is presented, together with the guidelines, for approval by the GAB.

12.1.2 Evidence-based instruments

Modern evidence-based guidelines often recommend different standardized quantitative and qualitative tools (scales, questionnaires) used by health-care professionals to diagnose illnesses and monitor treatment, and to help patients themselves to assess changes in their state of health.
For the successful implementation of the guideline, it may be necessary to translate into Estonian and validate the evidence-based instruments (scales and reflective tests) used to assess the patient’s condition, its severity and/or the effectiveness of treatment. Developing or translating evidence-based instruments is considered a part of the implementation process. The relevant instruments must be ready for use and publicly available as appendices to the guideline.

### 12.1.3 Guideline materials for patients and lay people

If recommendations are to be included in the guidelines that help patients to better cope with their health condition and its management, simple language versions of the recommendations are developed.

In addition to simple language recommendations, the Panel may decide that other information from the guideline should be provided to patients in order to ensure better implementation. In such cases, special information materials can be developed for independent use by the patient. Such materials, for instance in the format of an information leaflet will help the patient to better understand and follow certain recommendations in the guideline.

Making guideline recommendations easily understandable to patients, as well as providing them with helpful practical information facilitates better cooperation between health-care professionals and patients (and their loved ones), which is one of the key facilitators of guideline implementation, and thus also leads to better health outcomes for patients.

Simple language recommendations are prepared by the Guideline Secretariat. When additional information materials for patients are considered, first the Secretariat (with information also provided by the Panel) determines which information materials for patients on the same health topic have been previously published in Estonia. If the previously published information is in line with the developed guideline, the Panel decides whether creating new materials is justified. To develop patient information material, a working group within the Panel may be set up, and/or patients outside the Panel asked to provide feedback on the material at different stages of its development.

Any guideline materials addressed to patients (e.g. simple language recommendations and additional information material(s)) are presented to the Panel for feedback and endorsement. The Panel must ensure that the content is consistent with the guideline. Once approved by the Panel, the materials are tested on patients.
In the interest of diversity of feedback when identifying any potential issues in the recommendations and material(s), people with a history of the illness/condition addressed in the guideline (or their representatives) should be included, ensuring people of varying ages and with different social and educational backgrounds are consulted.

Feedback from patients is structured and documented, and necessary changes made in the recommendations and information material(s) by the Secretariat. The improved work, together with the feedback, is presented to the Panel, which takes a formal position on it and makes reasoned decisions in considering the recommendations or observations received. Based on these agreements, the work is supplemented, and a final version is submitted to the Panel for approval. Final versions of any guideline materials (including recommendations) addressed to patients are approved by the GAB, which receives the version approved by the Panel, accompanied by a summary of the patient feedback, and the decisions of the Panel. Materials for patients are then published, along with the guideline.

All materials for patients are produced in Estonian and also translated into Russian.
13. Implementation of the guidelines

In order to successfully implement guidelines, awareness and approval of them by health-care professionals, patients and other relevant parties must be achieved, and the activities in this regard must be thoroughly considered and detailed in the implementation plan. When developing a guideline, the Panel should consider simultaneously certain actions for implementation.

13.1 Implementation plan

The implementation plan is prepared by the Guideline Secretariat and approved by the Panel. It is added to the guideline after extensive discussion of all the responsibilities and needs (including scheduling) with the parties implementing the guidelines. The implementation plan, along with the guideline, is submitted to the GAB for approval (see Annex 19).

When developing an implementation plan, activities must be planned taking into consideration time constraints and requirements, along with the availability of the measurement and evaluation system, and the resources required for implementation. If necessary, the implementation process may be divided into several stages (for example, to accommodate local circumstances, or for other reasons). A specific checklist can be developed for guideline implementation planning, and supporting literature exists to assist with the process (35).

To prepare the implementation plan, certain steps should be carried out, as listed here.

- Aims and target groups of the implementation activities should be determined, considering the challenges of the current practice, new recommendations and target groups along with their characteristics/specifications.
- Possible barriers to implementation should be identified and a plan prepared of measures for overcoming them. The criteria for success should be defined, along with the indicators that describe them.
- The need for resources should be assessed. The resources required should be clearly indicated in the operational plan, including funding, staffing and time requirements.
- Notification needs must be assessed and planned. It should be considered how vital information reaches interested parties, and the relevant spokespeople should be identified to disseminate information about the guideline.
- Training should be identified and the necessary activities outlined, such as regular training sessions and online training.
- Existing structures and networks should be used for implementation. If possible, the implementation of the guideline should be included in the performance management system.
- The reference data of the indicators should be measured, ensuring that the data collected adequately reflect the current situation and provide a starting point for tracking further changes.
- The implementation process should be monitored by setting up a system for regular evaluation. Feedback should be given and a report submitted to the GAB within the agreed time frame.
- Clear roles and responsibilities should be defined for each activity.
- Milestones and a schedule should be set out for each implementation activity.

An example of an implementation plan can be found in Annex 19 and on the guidelines website.14

13.2 Indicators for assessing guideline implementation

In order to assess the implementation of guidelines, indicators are selected and added to the implementation plan. The indicators may be process indicators (e.g. frequency of prescription of specific drugs, length of hospital stay), outcomes (e.g. re-hospitalization for a particular reason), or clinical cases (e.g. patients with myocardial infarction). Processes or events that can be measured on the basis of health statistics or data received by the EHIF, along with audits or applied research in cooperation with universities or health-care institutions can also be used as indicators.

Upon the final selection of the indicators, the key stakeholders involved in the implementation of the guidelines should be consulted. Indicators and their measurement methodology are part of the implementation plan. The Panel confirms the indicators – in particular, for the final recommendations evaluated as being “strong” – to monitor the implementation of the health guideline and assess its impact. From among the indicators prepared by the Guideline Secretariat, the Panel selects those that are considered relevant in implementing the recommendations. Clinical indicators are confirmed within the implementation plan by the GAB. The EHIF compiles and monitors the results of the actual implementation of guidelines in medical practice.

14. Updating guidelines

When new knowledge, skills, and possibilities become available, the approved guidelines should be reviewed periodically to assess the extent of the need to update them. This need will arise if new evidence suggests any substantial change in the content of the current recommendations is needed; any organizational changes to the health-care system occur; or if assessing the implementation of the guidelines indicates a review of the recommendations is necessary. The process of updating guidelines should start no later than four years after their initial approval.

Review of the prepared guidelines is arranged by the Guideline Unit by requesting – at the latest during the fourth year after a guideline’s approval – an expert opinion from the Chair and/or the members of the Panel that prepared the existing guideline. The expert opinion distinguishes between the guideline’s health questions that would require the evidence to be updated, and other questions that have arisen in the meantime and which require further response.

The Guideline Unit, on the basis of expert opinions, provides the GAB annually with an overview of approved guidelines that need to be updated, together with proposals for the content and volume of the updates. In addition, the GAB considers the need to update the guidelines on the basis of the results of relevant statistics, audits or applied research, or based on feedback from interested parties (all attached to the proposal of the Guideline Unit).

Updating the guidelines may mean supplementing or modifying the scope. In addition to changing health questions, this also includes selecting essential outcomes, if they differ from those of the current guideline. The process of updating guidelines is based on the same principles and methodology as preparing a new guideline and should similarly be based on existing EtD frameworks.

In order to facilitate the updating procedure, the Guideline Unit must ensure the archiving and availability of key documents (including evidence summaries (SoF and EtD tables) and scientific literature used to develop the approved guidelines).
15. References


16. Annexes

16.1 Annex 1. Definitions and explanations

Adolopment

This is a new term in the epidemiological lexicon. Adolopment allows guidelines groups to capitalize on previous work and not have to repeat much of the arduous basic work that currently occurs when a new guidelines group is set up. It provides a structured approach to combine the advantages of selectively combining adoption, adaptation and de novo development of guideline recommendations, whether updated or new. The most important basis for updating is the existence of a trustworthy systematic review that can be then used for making judgements by the particular Guideline Panel. The efficiency of this process has also been greatly helped by the GRADE Evidence to Decision (EtD) frameworks that can be completed online.

Appraisal of Guidelines for Research and Evaluation (AGREE) instrument

This is a tool developed through international cooperation that provides a framework for assessing the quality of guidelines.¹

Algorithm

In the context of this handbook, an algorithm is a drawing illustrating the choices and recommendations described in the guideline.

Budget impact analysis

This enables evaluation of costs and impacts when interventions are implemented throughout the country. In order for it to be comprehensive, such an analysis must – in addition to assessing investments and potential savings at the level of doctors, health-care institutions and patients – take into account how many of these different actors are involved in the implementation of the intervention.

**Clinical guideline**

A clinical guideline documents systematically developed evidence-based recommendations on health-related activities. As a general rule, guidelines focus on one disease or condition and provide guidance for health-care professionals on how to diagnose and treat the condition, and/or recommendations for disease prevention. The information in the guideline informs choices between different interventions that affect health, treatment quality, and the use of health-care resources.

**Clinical (or health) question**

A clinical question is formulated using the PICO method. Questions (and answers) are provided by health-care professionals with the aim of obtaining information about patients and their conditions, the interventions carried out (or those that should have been), the current treatment and comparison with possible alternatives, and the achieved (or desired) outcomes.

**Cost analysis**

This is an analysis of the cost of two or more interventions that focus on the comparison of resource use and expected results.

**Evidence retrieved**

This is a methodical search for systematic reviews and research (in the form of materials from libraries or journals) relevant to a specific clinical question, resulting in the retrieval of a body of evidence, which is then reviewed.

**Evidence to Decision (EtD) framework or table**

This is a standardized approach to making recommendations that provides structure and transparency.

**Formal consensus**

This is a systematic method for reaching agreement in a working group (in this case among the Panel).
Guideline Advisory Board (GAB)

This is a body consisting of experts representing major stakeholders in the Estonian health system, responsible for the development of credible guidelines in Estonia. This includes overseeing the guideline development process, keeping the methodology updated, solving problems that have emerged during the process and managing any conflict of interest (COI).

Guideline Panel or guideline development group

The Guideline Panel is a body comprising external experts for a particular guideline with a central task to develop evidence-based recommendations according to the methodology and processes set out in this handbook.

Guideline Unit (at the University of Tartu)

The Guideline Unit is the team supporting the GAB and the various teams (both the Panel and the Secretariat) for the guidelines being developed. Members of the Guideline Unit operate as guideline development methodologists – ensuring that the guidelines are developed in accordance with the methodology and principles agreed upon in this handbook.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

GRADE is a method of coherent, reasonable and transparent assessment of evidence and recommendations; it is used by many international organizations.

GRADE profiles or Summary of Findings (SoF) tables

This is a tabular format for presenting synthesized information about intervention effects, diagnostic test accuracy (DTA), prognosis, values and preferences, or cost. It includes a rating of the certainty of evidence, sizes of effects in relative and absolute terms, measures of associations, DTA estimates or estimates of values, depending on the type of question asked.

Health Technology Assessment (HTA)

HTA is the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision-making regarding health technologies (pharmaceutical technologies, devices, etc.).
Implementation plan

An implementation plan outlines the dissemination, measurement and evaluation of the benefits of the guidance being provided. The plan should include analysis of possible barriers, success criteria and outcomes, baseline datasets, resources, training and educational needs. Other considerations within the plan include dissemination of information to relevant stakeholders and users, identification of existing mechanisms or networks, methods for monitoring implementation processes, reporting and feedback mechanisms, and milestones within the schedule.

Intervention

An intervention should weigh up the evidence-based options for the diagnosis, treatment and care of patients, taking into consideration disease prevention, drugs, surgical methods, patient education strategies and other treatment-related choices.

Outcome

The outcome is the planned changes in the state of health of the subjects or patients that may result from the causative factor or intervention.

PICO (patient/target group – intervention – comparator – outcome) method

This helps health-care professionals to remember the four questions that are most useful for formulating clinical/health questions and finding the right answers in assessing patient care. For a table describing the PICO method, see Table 6.1 in section 6.4 of this handbook.

Patients’ version

The patients’ version of a guideline is a tool designed for independent use by the patient. It may include information about the disease/condition its costs and prognosis, treatment, follow-up treatment and self-help techniques.

Peer review

Peer review is a thorough evaluation by experts in a field of scientific work, research, or health-care organizations.²

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Randomized controlled clinical trials

These are detailed planned studies that monitor the actual effects of treatment or interventions on patients. Targeted methods are used to reduce possible errors (including randomization and blind trials) and to allow comparison of interventions and control groups.

Recommendation

This is the direction recommended by a guideline, resulting from clinical questions and based on evidence.

Risk of bias assessment

This is a systematic analysis of the design and conduct of a clinical trial, resulting in bias (systematic error); that is, whereby the impact assessment is imprecise. This is also referred to as clinical trial quality assessment. Further details can be found in the Cochrane Handbook.3

Scope

The scope specifies the boundaries necessary for the development of guidelines. It is determined by the following aspects: patient/target group; medical care level; involved or abandoned interventions and treatments; information and support provided to patients and health-care professionals; the outcomes to be taken into account; and the relationship with other relevant guidelines.

Systematic review

This is an overview of scientific literature, which usually focuses on a particular clinical/health topic and responds to a specific research question. A systematic collection of specialized literature is carried out to identify all relevant studies. Published studies are evaluated, and the results are summarized on the basis of established criteria.

Topic

The topic specifies the disease or condition to be addressed by the guideline, as well as identifying the target group and the required level of medical/health care.

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16.2 Annex 2. Guideline Panel Chair checklist

Checklist for Guideline Panel chairs©

(https://heigrade.mcmaster.ca/guideline-development/chair-checklist)

v.3.2 | 20180130

Name of meeting:

Getting yourself prepared for the meeting

☐ Familiarize yourself with:
  ▪ the organization’s process and rules for guideline development;
  ▪ the organization’s policies for declaring and managing conflict of interest (COI);
  ▪ background material, particularly evidence tables and Evidence to Decision (EtD) tables;
  ▪ panellists, their areas of expertise and their declared COI;
  ▪ observers, technical staff and other meeting participants;
  ▪ controversial issues.

☐ Ensure involvement of Panel members in the question (PICO) development process.

☐ Ensure background material (particularly evidence tables and EtD tables) is disseminated to Panel members ahead of time for their review and input.

Getting the team prepared for the meeting

☐ Allow for sufficient face-to-face or video/remote meeting time with the technical team (coordinating team, systematic reviewers and guideline methodologists) before the meeting.

☐ Ensure meeting worksheets (e.g. EtD frameworks, including straw/mock recommendations – see below) are ready for the meeting in hard copies or online.

☐ Identify one or two people to record the minutes of the meeting. In addition, consider video or audio recording.

☐ Identify one person to edit to the EtD frameworks on a live screen. Instruct that person to refer to the Chair for final decisions or notes to record.

☐ Agree with the systematic review or knowledge synthesis team on what specific information to present (PICO question, summary of the search and its results, major results of the review, and evidence profile).
☐ Ask members of the technical team (particularly systematic reviewers) to address during the meeting any clarification questions from the Panel, but not to make any judgements or value-laden comments.
☐ Discuss how to conduct the voting.
☐ Assign someone to help with timekeeping if needed.

At the beginning of the meeting

☐ Clarify specific objectives/goals of the meeting and scope of the guidelines.
☐ Make appropriate acknowledgments.
☐ Introductions. As people introduce themselves, note names and seating of panellists.
☐ Solicit any new COI since they were last declared.
☐ Remind panellists about COI management policy, and that you will not allow strong advocacy, e.g.: “please state your point clearly once, and don’t keep hammering the same point. Everyone is clever enough to understand it from the first time, and to ask for clarification if they feel the need to”.
☐ Remind panellists about the confidentiality of the discussions, up to the point they are published or made public by the responsible parties, e.g. the organization.
☐ Clarify to panellists that they are expected not to ask after the meeting for changes in the quality of evidence or strength of recommendation agreed on during the meeting unless errors are apparent.
☐ Clarify ground rules (rules of process).
☐ Stress the importance of adhering to methodology and that “this is not the time to discuss its value”; for example, “you have accepted to be part of this game, so you need to play by its rules and not attempt to bend the rules”.
☐ Clarify who is a voting panellist, non-voting panellist, observer, technical advisor and other participants.
☐ Review the agenda and stress the importance of adhering to schedule.
☐ Check if Panel members are representing organizations; in most cases, even if selected from organizations, Panel members should use their own judgements.

Structuring the discussion

☐ Structure the discussion around the GRADE EtD frameworks (and the criteria that affect the final recommendation).
☐ Repeat the PICO at the beginning of each recommendation, present the straw recommendation, and work through the EtD criteria.
☐ Do not refer to or show recommendations made by other groups or guideline panels.
As panellists raise points that are relevant but not directly related to criteria that do not directly affect the recommendation, attempt to classify them as: conditions/key remarks to go underneath the recommendation statement; implementation considerations; monitoring considerations; implications for future research or other content of the EtD.

Show the straw or mock recommendation as a starting point for discussing the recommendation statement:
- e.g. for patients suspected of having tuberculosis (TB) who are smear negative, the WHO expert panel suggests/recommends using/not using test … over test … (conditional/strong recommendation … certainty in the evidence).

Building consensus

- When there seems to be a consensus on the direction of the recommendation (for versus against), agree on the direction first, then attempt to achieve consensus on its strength (strong versus conditional).
- When there seems to be a consensus on the strength of the recommendation (strong versus conditional), agree on that strength by consensus.
- In trying to achieve consensus among panellists:
  - check first whether there is agreement by allowing anyone on the Panel to speak;
  - if there seems to not be agreement, highlight the disagreement; clarify what people are agreeing on and what they are disagreeing on; and check whether those disagreeing would be willing to accept the majority’s opinion (e.g. “can you live with it?”);
    - if not, ask whether a modification or addition would enable them to agree;
    - if not, resort to voting; in the case of voting, keep a record and note results.

Managing COI

- Enforce the COI management strategy.
- Stay alert to strong advocacy (e.g. aggressive argumentation, leading statements, repeating the same point).
- When you detect strong advocacy, highlight it in front of the Panel and ask the person of interest to cease strong advocacy; also consider reminding the group about the specific COI in front of the Panel.
- Repeat the statement about confidentiality (in particular, if the meeting is lasting more than one day).
- Avoid statements that reflect your own views on the matters being discussed; aim to show neutrality.
**Additional points for the meeting**

- Enforce timekeeping.
- Note to minute-taker important points to go in the meeting report or guideline document; this is particularly relevant when you need to ensure transparency.
- Clarify conceptual issues as needed.
- Ensure everyone has the chance to participate, particularly community/patient representatives.
- Allow for time to debrief with the technical team during the meeting at regular intervals and as needed.

**At the end of the meeting**

- Summarize what has been achieved.
- Agree on what needs to be achieved after the meeting.
- Clarify the communication plan.
- Make appropriate acknowledgments.
- Repeat the statement about confidentiality of discussion (describe what should remain confidential and what can be made public in agreement with relevant organizations).
- Let the panellists know that they may be receiving a survey for feedback and evaluation (when applicable).

**After the meeting**

- Send a follow-up message the day after the meeting summarizing the positive aspects of the meeting and accomplishments.
- Provide summary information in writing about what is next.
### 16.3 Annex 3. Guideline participant tool

**Guideline Participant Orientation Tool (GPOT)* (v6)**
https://heigrade.mcmaster.ca/guideline-development/guideline-participants

#### 1. Preparations – before you join a guideline development group meeting

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<tbody>
<tr>
<td>1.1</td>
<td>Be clear on the guideline group objectives, deliverables and timeline.</td>
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<tr>
<td>1.2</td>
<td>Commit to attending all conference calls and in-person meetings. If you are not able to attend, this should be explicitly mentioned to the guideline sponsor in advance.</td>
</tr>
<tr>
<td>1.3</td>
<td>Be clear on what role you are taking within the guideline group and how much time is required to fulfil this role. Understand the experience, knowledge or training that is expected for the role you are filling. For more information on guideline group membership see the guideline group membership section of the GIN-McMaster Guideline Development Checklist and the Participant Roles document for your guideline group.</td>
</tr>
<tr>
<td>1.4</td>
<td>Accurately represent your content knowledge and methodological skills to the guideline sponsor (e.g. basic statistics, clinical epidemiology, assessing risk of bias, rating quality of evidence according to the GRADE process).</td>
</tr>
<tr>
<td>1.5</td>
<td>Familiarize yourself with guideline methodology that the group will use for moving from evidence to recommendations. Guideline sponsors may have specific preparation materials or handbooks for training. For GRADE methodology training, see the McMaster GRADE Online Learning Modules. For WHO guidelines, see the WHO Handbook for Guideline Development.</td>
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<tr>
<td>1.6</td>
<td>Complete the declaration/conflict of interest (DOI/COI) as requested by the guideline sponsor in an honest, timely and transparent manner, in advance of the meeting. For more information on DOI/COI considerations, see the GIN-McMaster Guideline Development Checklist.</td>
</tr>
<tr>
<td>1.7</td>
<td>If your DOI should change at any point in the guideline development process, provide changes in writing as soon as possible.</td>
</tr>
<tr>
<td>1.8</td>
<td>Understand that participation in the guideline group may be made public as part of guideline transparency.</td>
</tr>
</tbody>
</table>

4 GIN: Guidelines International Network.
| 1.9 | Ensure you have a firm understanding of the guideline question(s) addressed in the guideline – often in the PICO (Population, Intervention, Comparator, Outcome) question-framing format. If you have any concerns about the question these should be clarified prior to the meeting. For more information on PICO question generation see the GIN-McMaster Guideline Development Checklist. |
| 1.10 | Prepare for all meetings, including conference calls by reviewing distributed materials (e.g. minutes from previous meetings or terms of reference) in advance. |
| 1.11 | Review the evidence summarized in draft systematic reviews conducted. In particular, provide feedback as early as possible if you disagree with any evidence that has been included or omitted. For more information on the inclusion of evidence see the GIN-McMaster Guideline Development Checklist. |
| 1.12 | If at this stage or at any other stage of the guideline development process you have any concerns, express these to the Chair or co/vice-Chair and/or the guideline sponsor so that they can be appropriately addressed according to the sponsor’s rules. Refrain from hidden criticism that can undermine the group process. |

### 2. Meetings – considerations during guideline group meetings

| 2.1 | Ensure that the process, methods, and agenda are clear to you. Ask any questions of clarification at the outset of the meeting. For more information on the guideline group process see the GIN-McMaster Guideline Development Checklist. |
| 2.2 | The Chair will conduct introductions at the beginning of each meeting. If there is any doubt about the role of any guideline group participants, you should seek clarification. |
| 2.3 | Avoid any undue interruption of the guideline development process. Arrive on time for all meetings and conference calls. Where extenuating circumstances arise, inform the guideline group sponsor/Chair at the earliest opportunity. If you have any urgent business or phone calls that need to be attended to during a meeting, please step outside to avoid disrupting the group. |
| 2.4 | Adhere to methods that have been endorsed by the guideline sponsor, unless otherwise advised (e.g. GRADE). |
2.5 | Refer to the PICO question that is being addressed to ensure that you and the group stay on task.

2.6 | Through the course of the meeting, adhere to the contribution rules for your specific role (e.g. if you are an observer, do not contribute unless you are specifically requested to do so). See the Participant Role definitions provided.

2.7 | Unless specifically asked to represent an organization in the guideline group, your contributions should be made from your perspective, not on behalf of an organization.

2.8 | Contribute your perspectives to the discussions when appropriate. Remember that you were chosen specifically for your expertise or the perspective you represent. If you do not contribute, your perspective will be lost.

2.9 | Speak only when the Chair calls on you – avoid interrupting other members.

2.10 | When you do speak, please ensure that you speak clearly so that everyone can hear you and stick to the point of the current topic of discussion.

2.11 | When vocalizing an opinion, ensure you have the evidence and/or a clear rationale to back up your opinion. Speak only based on the evidence reviewed during the meeting or explicitly referenced in the guideline process.

2.12 | Contribute to the discussions in a fair and equitable manner. Be succinct and direct with your contributions, and be respectful to others so that all may have an opportunity to contribute.

2.13 | Be attentive and mindful of meeting schedule. Assist the Chair in keeping the discussions on time and on topic. Where the Guideline Panel Chair has indicated that a discussion on a topic is closed, abide by this request.

2.14 | When there is no agreement by consensus for a topic, a vote may be carried out according to rules set out by the Panel Chair and/or sponsor. Participants with a DOI deemed in conflict with the topic should abstain from the vote according to the sponsor’s rules.

2.15 | If asked to present material to the guideline group, please consider the following presentation suggestions: prepare and submit slides or handouts ahead of the meeting to the responsible parties; adhere to the time allotted for the presentation; make your presentation brief and minimize the recounting of information that has already been reviewed by guideline Panel members; present material objectively and do not make leading statements unduly influenced by your opinion on the evidence.
### 3. Follow-up – after guideline group meetings

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Maintain confidentiality as per agreed-upon procedures, including abiding by data or content embargoes as relevant. Typically, the content of guidelines can only be discussed after formal publication or with explicit permission by the sponsoring organization.</td>
</tr>
<tr>
<td>3.2</td>
<td>Do not undermine the guideline development process by incorporating new evidence or attempting to change the quality of evidence or the strength of recommendations after the guideline group meeting, without explicit permission from the guideline sponsor organization and guideline group members.</td>
</tr>
<tr>
<td>3.3</td>
<td>Review meeting minutes for discrepancies and provide feedback in a timely fashion.</td>
</tr>
<tr>
<td>3.4</td>
<td>If requested, conduct a thorough review of draft guideline documents.</td>
</tr>
<tr>
<td>3.5</td>
<td>If requested to contribute to the guideline writing process, please consider these suggestions: focus on the specific writing task given, meet deadlines requested, use written language and style for clear and effective communication to end-users (this includes avoiding excessive use of acronyms/abbreviations). For guidance on wording and reporting in guideline publications see the <a href="#">GIN-McMaster Guideline Development Checklist</a>.</td>
</tr>
<tr>
<td>3.6</td>
<td>If requested, assist the sponsoring organization with the publication, promotion, dissemination and evaluation of the guideline. For more information see the <a href="#">GIN-McMaster Guideline Development Checklist</a>.</td>
</tr>
</tbody>
</table>

*Note: This tool is designed to be comprehensive and modular. Three modules are designed to identify steps participants should consider or take in the (i) preparation phase, (ii) during guideline group meetings and (iii) in follow-up. For specific guideline committees or at certain stages in the process, only relevant sections should be used. The online version of this tool is designed to filter based on the guideline contributor role.*
16.4 Annex 4. Example of an Evidence to Decision (EtD) framework: Estonian sepsis guideline

Source: GRADEpro GDT (2015).\textsuperscript{5}

\textsuperscript{5} GRADE working group. GRADEpro GDT [website]. Hamilton (ON): McMaster University; 2015 (http://gradepro.org/, accessed 3 January 2018).
16.5 Annex 5. Form for declaration of interest (DOI) and confidentiality

For this DOI, you are asked to disclose economic, professional or other interests that may in fact, or in effect, affect the proper performance of your duties related to the preparation of the clinical guidelines; that is, there may or may not be a conflict between obligations and private interests.

You are also asked to declare the relevant interests of those connected to you who may, or who are thought to be, adversely affecting your decision-making, such as close family members, employers, close associates, or other people with whom you have significant common personal, financial or professional interests.

You are asked to give consent that any significant interests may be disclosed to the participants in the guideline development process and presented in the minutes of the meetings.

You are also asked to keep all information and decisions and any other aspects related to this work confidential unless permission has been given by the GAB or what you disclose has been publicly released.

[First and last name]

<table>
<thead>
<tr>
<th>Interest to be declared</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Work relations and counselling:</strong> have you received remuneration from pharmaceutical and medical companies over the past 2 years, including fees for expert advice and/or counselling?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>2. Research grant:</strong> has your institution or research unit received support or funding from pharmaceutical and medical companies over the last 2 years?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>3. Public views and positions:</strong> have you been in a paid or unpaid profession for the past 2 years, or have you worked in another role, in which you were expected to represent or defend your position regarding clinical guidelines?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>4. Additional information:</strong> to the best of your knowledge, does the guideline benefit people with whom you have shared personal, financial or professional interests, or have an adverse effect on them? (This means your close family members and close colleagues.)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
[If yes, list all relevant companies and organizations]

................................................................................................................................
................................................................................................................................

DECLARATION.

I confirm that to the best of my knowledge, the above data are correct and complete. If the above information changes, I will inform the parties concerned and complete a new DOI reflecting the changes. Such changes include all those that occur before or during the meeting, and until the final results are published.

Date: ________________  Signature: _____________________
16.6 Annex 6. Template for topic proposal

Topic proposal

<table>
<thead>
<tr>
<th>1. The title of the guideline to be prepared</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>2. The need to develop a guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Including links to national health-care priorities and clinical guidelines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Patients/target group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/target group(s) covered by the guideline, and excluded subgroups (age groups).</td>
</tr>
</tbody>
</table>

Example 1.
People with a particular type of illness: adult patients with hypertension who are being monitored by a family doctor. Patients who have previously been diagnosed with cardiovascular pathology and/or diabetes are included. Elderly patients (aged over 75 years of age) are included. Children aged under 18 years and pregnant women are excluded.

Example 2.
Obese patients aged 18 years and over.

Example 3.
Adults with disorders affecting motor activity, movement, speech, swallowing, bladder and/or intestinal function, cognitive function, and other disorders caused by stroke (I60-I69).

Example 4.
Patients at risk of bed sores who are in care homes or nursing homes, including bedridden patients, wheelchair users, and people with reduced mobility.

<table>
<thead>
<tr>
<th>4. Burden of disease in Estonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of patients/size of the target group with the disease or condition in Estonia (morbidity, prevalence, mortality, etc.) and the impact on the Estonian health- and social-care system.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Differences in treatment practices and/or health outcomes and/or costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Significant differences in treatment practices in different regions of Estonia and among health-care providers and/or levels of care (e.g. primary care versus specialist medical care) and in the treatment of patients/target groups (including subgroups), or by different cost categories (drugs, inpatient treatment, etc.).</td>
</tr>
<tr>
<td>- The difference in medical practice in Estonia in comparison with international practice.</td>
</tr>
</tbody>
</table>
6. **The expected impact on the health indicators of the patient and/or the use of resources**

Provide measurable examples, taking into account the following elements:
- modernizing current practices
- the presence of new interventions (including diagnostic studies and services)
- the availability of new evidence-based practice, possibly altering current practice
- more efficient use of resources.

7. **The main users of the guideline**

Areas or levels of health care in which the guideline is mainly applied.

<table>
<thead>
<tr>
<th>general medical care</th>
<th>specialist medical care</th>
<th>emergency medicine</th>
<th>other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>__________________________</td>
</tr>
</tbody>
</table>

The main user:

8. **Topics NOT addressed by the guideline**

For example:
- screening and prevention of hypertension (covered by another clinical guideline)
- smoking (covered by another clinical guideline)
- secondary hypertension
- prevention and reduction of overweight by conservative methods
- hypertensive crisis and first aid

9. **Clinical issues or problems that need to be addressed**

[See Chapter 7 of the Guideline Handbook]

What causes the problem? What happens if someone has this problem? How often does the problem occur? The patients with which diagnoses have this problem? How can this problem be prevented? How is this problem diagnosed and/or treated? Which health-care measures should be taken to solve this problem? What are the expected results of intervention?

10. **Specialties consulted with the commentary of the person in charge**

For example: Estonian Society of Cardiology, Estonian Nurses Union, etc. This can also be presented as a stand-alone document. A (digitally) signed document is preferred.

11. **Contact details of the topic initiator.**

Provide the name of the topic initiator and their e-mail and/or postal address.

(Digital) Signature: __________________________ Date: ____________
16.7 Annex 7. Form for defining the scope of a guideline

Scope approved on: [date]

<table>
<thead>
<tr>
<th>Guideline title</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Target group of users</td>
<td></td>
</tr>
<tr>
<td>People/patients and subgroups covered</td>
<td></td>
</tr>
<tr>
<td>Topics addressed by the guideline</td>
<td></td>
</tr>
<tr>
<td>Topics NOT addressed by the guideline</td>
<td></td>
</tr>
<tr>
<td>Other relevant clinical guidelines in Estonia</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Very important: Important:</td>
</tr>
</tbody>
</table>

Structure of the guideline or topics addressed:

Abbreviations:

Definitions:

Clinical questions:

1. Question

<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
</table>

What problem does the question seek to solve?

2. Question

<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
</table>

What problem does the question seek to solve?

3. Question

<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
</table>

What problem does the question seek to solve?

(Digital) Signature: Date:
16.8 Annex 8. Topic selection evaluation criteria examples

The problem statement and the purpose of the guideline

Example 1. The care of patients with stroke in the acute period must be optimal in order to improve the patient’s prognosis and prevent the risk of recurrence of stroke and the related costs of social assistance.

Example 2. HIV-positive patients not receiving or not adhering to treatment are infectious, so the number of new infections is not decreasing in society. Early diagnosis of the disease requires organizing HIV testing principles and expanding HIV testing in the population. The goal is the earliest possible detection in HIV-positive people. HIV testing has been recently extended to the primary care level (decentralized).

Example 3. Sepsis and its more severe manifestations – severe sepsis and septic shock – are important issues in the health-care system that require prompt action and a massive amount of human and material resources.

Burden of disease in Estonia

Example 1. In many developed countries, stroke is second or third highest among the causes of death, as well as a significant cause of disability. Epidemiological studies in Estonia have shown that the first incidence of stroke is high compared to other countries. The first incidence of stroke in Estonia is 230 people per 100,000 and the 30-day lethality is 26% (according to an epidemiological study carried out in Tartu in 2001–2003). About one third of patients are aged under 65 years. Owing to population growth and ageing, the burden of stroke is rising globally, despite a decline in morbidity and mortality.

Example 2. Over the years, a total of 9281 people have been diagnosed with HIV in Estonia, including 455 people with AIDS. In 2015, 270 new cases of HIV infection were discovered. Most of the HIV-positive people registered in 2015 were aged 20–39 years (67.4%). In 2015, no HIV-positive neonates were registered. The proportion of people aged over 40 years is increasing year on year. In 2008 they represented 14.5% of the total number; in 2015 they represented 30.4%. Over the years, the gender structure of HIV infection has also changed; in recent years the proportion of women has remained stable, accounting for about 40% of the total number of infected people. The supposed paths/risk factors are known in 60% of the HIV-positive cases detected in 2015: parenteral transmission (injection of narcotic substances) – 46 (17.0%); heterosexual sexual activity – 75 (27.8%); homosexual sexual activity – 17 (6.3%); unspecified sexual path – 22
(8.1%). The average indicator of new HIV cases per 100,000 inhabitants (as of 2014) in the European Union (EU) was 5.9 and in it was Estonia 20.6. The number of HIV-positive people being monitored is 5,513; of these, 37 are children. A total of 2,998 are receiving antiretroviral (ARV) treatment. The median annual cost of medication for a single human ARV treatment regimen is €2,500. In addition to ARV treatment, HIV-positive people also need medical services (diagnostic tests, appointments with medical specialists, and hospital care). Based on the Estonian Health Insurance Fund (EHIF) database, in 2014, the average annual health-care cost per patient was €333, while the cost of treatment of HIV-positive patients in the same age group (20–59 years) was €1,202 per patient; 3.6 times higher than in the general population. The treatment costs for AIDS patients was also three times higher in comparison with a patient who had not yet developed AIDS.

**Example 3.** The overall global mortality rate for sepsis is estimated at 6.7%, while the mortality rates in cases of its severe forms – severe sepsis and septic shock – are 20% and 45%, respectively. Data are not readily available from the EHIF on the cost of treating sepsis, because it is a complex syndrome that is treated across a variety of specialties, and its care requires the use of a variety of health-care services. According to the audit of severe sepsis and septic shock performed in 2015, 52% of the patients were aged over 70 years. The most common causes were respiratory, urinary tract, and gastrointestinal infections. The hospital mortality rate of the sample was 42.4% and the mortality rate after six months was 59.2%.

**Differences in practices and/or health outcomes and/or costs**

**Example 1.** The audit (2010) and follow-up audit (2013) of stroke in Estonia have shown that stroke treatment improved somewhat over the period between audits, but the improvement is uneven across Estonian inpatient care settings. Owing to the absence of a 24-hour watch by a neurologist, one central hospital does not have the capacity to treat stroke patients round the clock. There are also differences in treatment facilities; diagnostics and treatment in general hospitals are lacking, in that these facilities do not currently meet the requirements for the treatment of patients presenting with acute stroke. The follow-up (2013) audit presented a proposal to modernize the Estonian stroke treatment clinical guidelines.

**Example 2.** Problems include: late diagnosis of HIV; a large proportion of infected patients begin treatment late; and, in many cases, they do not adhere to the treatment regimen or discontinue long-term treatment. A study performed by the University of Tartu estimated that only 29% of diagnosed HIV-positive patients receive treatment, and 19% of those with a reduced viral load are diagnosed at a
late stage. However, HIV-positive people who are diagnosed late are costly for the health system, as their treatment involves more expensive regimens and they often already have health problems that require special attention. In addition, the lack of patient compliance and discontinuation of treatment makes further treatment more expensive, and there is a risk of patients building a resistance to the drugs.

Example 3. The clinical audit conducted in 2015 evaluated the treatment of sepsis patients in Estonian active treatment hospitals. There were significant gaps in terms of taking blood cultures and initiating antibacterial therapy.

The expected impact on the health indicators of the patient and/or the use of resources

Example 1. Decreased lethality is expected through the reduced risk of recurrence of stroke. The functional capacity of patients that have survived stroke is also expected to improve, leading to the return to work of patients of working age and a reduction in the need for care.

Example 2. With early detection, provision of treatment and proper adherence to treatment regimens, the spread of HIV stops. More effective HIV testing and treatment referral help to detect more people with HIV infection. In 95% of cases, the risk of infection decreases when the HIV-positive person receives treatment and, accordingly, there is a significant reduction in the risk of infection of partners, which could stop or control the spread of HIV. It also reduces the proportion of expensive treatment at a later stage and diminishes the risk of complications. The capacity for work of HIV-positive patients undergoing treatment is maintained. Ensuring compliance with and consistency of treatment by using medicines to treat side-effects, organizing better treatment, and so on, not only reduces the use of more expensive treatment regimens but also combats the emergence of drug resistance. It is possible to use a system of joint procurement of HIV testing equipment, potentially resulting in lower prices.

Example 3. An updated treatment guide will modernize the principles of sepsis treatment in Estonia, thereby improving the current treatment outcomes. Measurable parameters include: the mortality rate for 30 days and 90 days; the proportion of blood cultures collected during the first hour of hospitalization; and the proportion of antibiotics administered.
### Annex 9. Table format for mapping guidelines to scope questions

**Availability of evidence (example form)**

<table>
<thead>
<tr>
<th>No</th>
<th>Name of paper</th>
<th>Assessor</th>
<th>Scope question #1</th>
<th>Scope question #2</th>
<th>Scope question #3</th>
<th>Scope question #4</th>
<th>Scope question #5</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Guideline 1</td>
<td>Name 1</td>
<td>No info</td>
<td>No info</td>
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<td>No info</td>
<td>No info</td>
</tr>
<tr>
<td>2</td>
<td>Guideline 2</td>
<td>Name 2</td>
<td>Yes pp. 2–4</td>
<td>Yes table on p. 3</td>
<td>No info</td>
<td>No info</td>
<td>Maybe pp. 7–8</td>
</tr>
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</table>
### Annex 10. Useful resources

<table>
<thead>
<tr>
<th></th>
<th>Website</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific literature databases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PubMed</td>
<td><a href="https://pubmed.ncbi.nlm.nih.gov/">https://pubmed.ncbi.nlm.nih.gov/</a></td>
<td>Published medical and scientific literature database</td>
</tr>
<tr>
<td>The Cochrane Library</td>
<td><a href="http://www.cochranelibrary.com/">http://www.cochranelibrary.com/</a></td>
<td>Database of systematic overviews</td>
</tr>
<tr>
<td><strong>Clinical guideline databases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estonian clinical guidelines (in Estonian or Russian)</td>
<td><a href="http://ravijuhend.ee/">http://ravijuhend.ee/</a></td>
<td><a href="http://ravijuhend.ee/">http://ravijuhend.ee/</a></td>
</tr>
<tr>
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<td><a href="http://dbep.gradepro.org/">http://dbep.gradepro.org/</a></td>
<td>Database of EtD frameworks</td>
</tr>
<tr>
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<td><a href="http://www.g-i-n.net/library">http://www.g-i-n.net/library</a></td>
<td>International guideline library</td>
</tr>
<tr>
<td>National Guideline Centre</td>
<td><a href="https://www.replondon.ac.uk/national-guideline-centre-ngc">https://www.replondon.ac.uk/national-guideline-centre-ngc</a></td>
<td>Clinical guidelines developed by NICE (platform hosted by the Royal College of Physicians in United Kingdom)</td>
</tr>
<tr>
<td>SIGN</td>
<td><a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a></td>
<td>Clinical guidelines prepared for the Scottish health system</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td><a href="https://www.nccn.org/">https://www.nccn.org/</a></td>
<td>Clinical guidelines for cancer (United States)</td>
</tr>
<tr>
<td><strong>Instruments for assessing the quality of published research, analyses and guidelines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROBIS</td>
<td><a href="http://www.bristol.ac.uk/social-community-medicine/projects/robis/robis-tool/">http://www.bristol.ac.uk/social-community-medicine/projects/robis/robis-tool/</a></td>
<td>Assessment of the methodological quality of systematic reviews</td>
</tr>
<tr>
<td>CONSORT</td>
<td><a href="http://www.consort-statement.org/">http://www.consort-statement.org/</a></td>
<td>Assessment of the methodological quality of randomized clinical trials</td>
</tr>
<tr>
<td>STROBE</td>
<td><a href="http://www.strobe-statement.org/">http://www.strobe-statement.org/</a></td>
<td>Assessment of the methodological quality of monitoring studies</td>
</tr>
<tr>
<td>AGREE</td>
<td><a href="https://www.agreetrust.org/practice-guidelines/">https://www.agreetrust.org/practice-guidelines/</a></td>
<td>Assessment of the methodological quality of clinical guidelines</td>
</tr>
<tr>
<td>Drummond Criteria</td>
<td><a href="https://www.nlm.nih.gov/nichsr/edu/healthcon/drummond_list.html">https://www.nlm.nih.gov/nichsr/edu/healthcon/drummond_list.html</a></td>
<td>Assessment of the quality of economic evaluations</td>
</tr>
</tbody>
</table>
16.11 Annex 11. Examples of search strategies

<table>
<thead>
<tr>
<th>What is the clinical disease?</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question or definition for the search:</td>
<td>Are there guidelines for hypertension?</td>
</tr>
</tbody>
</table>


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


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, follow the steps outlined in this example.

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 is detailed below. In the event that PubMed cannot be accessed or another search database is being used, the same text below serves as an example of the type of search strategy that must be written in order 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
(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
If the search does not yield (enough) guidelines or systematic reviews, the next search would be for randomized controlled trials.

**Example 3. Searching for randomized controlled trials**

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

16.12  Annex 12. ROBIS instrument\textsuperscript{6}

Phase 1: Assessing relevance (Optional)

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

For intervention reviews:

<table>
<thead>
<tr>
<th>Category</th>
<th>Target question (e.g. overview or guideline)</th>
<th>Review being assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Population(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome(s):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For aetiology reviews:

<table>
<thead>
<tr>
<th>Category</th>
<th>Target question (e.g. overview or guideline)</th>
<th>Review being assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/Population(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure(s) and comparators:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome(s):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For DTA reviews:

<table>
<thead>
<tr>
<th>Category</th>
<th>Target question (e.g. overview or guideline)</th>
<th>Review being assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index test(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference standard:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target condition:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For prognostic reviews:

<table>
<thead>
<tr>
<th>Category</th>
<th>Target question (e.g. overview or guideline)</th>
<th>Review being assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome to be predicted:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intended use of model:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intended moment in time:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Phase 2: Identifying concerns with the review process

**DOMAIN 1: STUDY ELIGIBILITY CRITERIA**

Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:

<table>
<thead>
<tr>
<th>Question</th>
<th>Y/PY/PN/N/NI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Did the review adhere to pre-defined objectives and eligibility criteria?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>1.2 Were the eligibility criteria appropriate for the review question?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>1.3 Were eligibility criteria unambiguous?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>1.4 Were any restrictions in eligibility criteria based on study</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>characteristics appropriate (e.g. date, sample size, study quality,</td>
<td></td>
</tr>
<tr>
<td>outcomes measured)?</td>
<td></td>
</tr>
<tr>
<td>1.5 Were any restrictions in eligibility criteria based on sources of</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>information appropriate (e.g. publication status or format, language,</td>
<td></td>
</tr>
<tr>
<td>availability of data)?</td>
<td></td>
</tr>
</tbody>
</table>

Concerns regarding specification of study eligibility criteria

Rationale for concern:

**DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**

Describe methods of study identification and selection (e.g. number of reviewers involved):

<table>
<thead>
<tr>
<th>Question</th>
<th>Y/PY/PN/N/NI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Did the search include an appropriate range of databases/electronic</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>sources for published and unpublished reports?</td>
<td></td>
</tr>
<tr>
<td>2.2 Were methods additional to database searching used to identify</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>relevant reports?</td>
<td></td>
</tr>
<tr>
<td>2.3 Were the terms and structure of the search strategy likely to retrieve</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>as many eligible studies as possible?</td>
<td></td>
</tr>
<tr>
<td>2.4 Were restrictions based on date, publication format, or language</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>appropriate?</td>
<td></td>
</tr>
<tr>
<td>2.5 Were efforts made to minimize error in selection of studies?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
</tbody>
</table>

Concerns regarding methods used to identify and/or select studies

Rationale for concern:

**DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**

Describe methods of data collection, which data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:

<table>
<thead>
<tr>
<th>Question</th>
<th>Y/PY/PN/N/NI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Were efforts made to minimize error in data collection?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>3.3 Were all relevant study results collected for use in the synthesis?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>3.5 Were efforts made to minimize error in risk of bias assessment?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
</tbody>
</table>

Concerns regarding methods used to collect data and appraise studies

Rationale for concern:

Notes. Y = yes; PY = probably yes; PN = probably no; N = no; NI = no information.
**DOMAIN 4: SYNTHESIS AND FINDINGS**

Describe synthesis methods:

<table>
<thead>
<tr>
<th>4.1</th>
<th>Did the synthesis include all studies that it should?</th>
<th>Y/PY/PN/N/NI</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>Were all pre-defined analyses reported or departures explained?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>4.3</td>
<td>Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>4.4</td>
<td>Was between-study variation (heterogeneity) minimal or addressed in the synthesis?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>4.5</td>
<td>Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
<tr>
<td>4.6</td>
<td>Were biases in primary studies minimal or addressed in the synthesis?</td>
<td>Y/PY/PN/N/NI</td>
</tr>
</tbody>
</table>

Concerns regarding the synthesis and findings

Rationale for concern: LOW/HIGH/UNCLEAR

**Phase 3: Judging risk of bias**

Summarize the concerns identified during the Phase 2 assessment:

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

**RISK OF BIAS IN THE REVIEW**

Describe whether conclusions were supported by the evidence:

| A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? | Y/PY/PN/N/NI |
| B. Was the relevance of identified studies to the review’s research question appropriately considered? | Y/PY/PN/N/NI |
| C. Did the reviewers avoid emphasizing results on the basis of their statistical significance? | Y/PY/PN/N/NI |

Risk of bias in the review

Rationale for risk: RISK: LOW/HIGH/UNCLEAR

Notes. Y = yes; PY = probably yes; PN = probably no; N = no; NI = no information.
16.13 Annex 13. Examples of results of the search for recommendations and systematic reviews

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 2–10/2.4–5.0 mmHg) of the potential benefit salt reduction could have on blood pressure.

Notes. VHA: Veterans Health Administration; BHS: British Hypertension Society; CMA: Competition and Markets Authority; SIGN: Scottish Intercollegiate Guidelines Network; ICSI: Institute for Clinical Systems Improvement; JNC: Joint National Committee; NZ: New Zealand (guidelines group); SA: SA Health (Government of South Australia); ESH: European Society of Hypertension.

Systematic reviews

A meta-analysis of 56 trials 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 mmHg in hypertensive patients. No significant effect was seen in diastolic pressure. Decreases in blood pressure were larger in trials of older hypertensive individuals.


A meta-analysis of 17 trials in individuals with elevated blood pressure (n=734) was carried out. 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% confidence interval (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 3–12 g/day, the lower the salt intake achieved, the lower the blood pressure.

### 16.14 Annex 14. Examples of reporting single studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patients</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Duration</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iles &amp; Emerson (1974); study period: 1965–1973</td>
<td>32 adult patients. Diagnosis following excisional biopsy in 30 and fine needle aspiration in 2.</td>
<td>13 episodes treated by surgery alone or with Streptomycin. The remainder treated with surgery and chemotherapy, or chemotherapy alone.</td>
<td>In 2 patients, fresh nodes appeared during therapy.</td>
<td>Mean follow-up 10 years after treatment with surgery alone revealed relapses in 12 cases. 5.5 year follow-up after surgery with chemotherapy; no relapses.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 16.15 Annex 15. GRADE evidence profile

Should empiriliselt monoteraapia vs. 2 antibakteriaalse ravimi kombinatsiooni be used for sepsise või septiilse õoku neutropeen?**

- **Empliriliselt monoteraapia võrreldes 2 antibakteriaalse ravimi kombinatsiooniga septiilse õoku neutropeenilistel patsientide tal**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td><strong>No of patients</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Suremuse vähemine SSC Paul metaanalüüs (palavikuiga neutropeenia pahaloomise kasvajaga patsiendid, sama beetalakaamantibiootikum mõlemas gruppis)

| 11 | randomised trials | not serious | not serious | serious | not serious | none | 49,825 (5.3%) | 70,893 (7.8%) | RR 0.74 (0.55 to 1.06) | 20 fewer per 1.00 (from 37 fewer to 5 more) | MODERATE | KRITILINE |

#### Suremuse vähemine Sjövall metaanalüüs (raske sepsisega intensivravikonna patsiendid)

| 13 | randomised trials | not serious | not serious | serious | not serious | none | 235/1106 (21.2%) | 269/1161 (23.2%) | RR 1.11 (0.95 to 1.29) | 25 more per 1.00 (from 12 fewer to 67 more) | MODERATE | KRITILINE |

#### Suremuse vähemine SSC Paul metaanalüüs (sepsisega patsiendid, sama beetalakaamantibiootikum mõlemas gruppis) (follow up: mees 30 days)

| 15 | randomised trials | not serious | not serious | serious | serious | publication bias strongly suspected | 76/716 (10.6%) | 80/715 (11.2%) | RR 0.97 (0.73 to 1.30) | 3 fewer per 1.00 (from 30 fewer to 34 more) | VERY LOW | KRITILINE |

*Source: authors’ own compilation.*
### 16.16 Annex 16. GRADE SoF table in Estonian

#### Empiiriliselt monoterapiaat võrreldes 2 antibakteriaalse ravimi kombinatsiooni septilise šokiga neutropeenilistel patienidel

**Patient or population:** sepsise või septilise šokiga neutropeenilistel patienidel

**Intervention:** empiiriliselt monoterapiaat

**Comparison:** 2 antibakteriaalse ravimi kombinatsiooni

**Outcomes**

<table>
<thead>
<tr>
<th>№ of participants (studies) Follow-up</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Risk with 2 antibakteriaalset ravimi kombinatsiooni</th>
<th>Risk difference with empiiriliselt monoterapiaat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suremuse vähemine SSC Paul metaanalüüs (palavikuga neuptrade pahaloomuse kasvajaga patsientidel, sama beetaalaktaamantbiotookum mõlemas grupis)</strong></td>
<td>1718 (11 RCTs)</td>
<td>MODERATE a,b</td>
<td>RR 0.74 (0.53 to 1.06)</td>
<td>78 per 1,000 (37 fewer to 5 more)</td>
</tr>
<tr>
<td><strong>Suremuse vähemine Sjövall metaanalüüs (raske sepsisega intensiivraviosakonna patsiendid)</strong></td>
<td>2267 (13 RCTs)</td>
<td>MODERATE c</td>
<td>RR 0.11 (0.95 to 1.29)</td>
<td>232 per 1,000 (12 fewer to 67 more)</td>
</tr>
<tr>
<td><strong>Suremuse vähemine SSC Paul metaanalüüs (sepsisega patsiendid, sama beetaalaktaamantbiotookum mõlemas grupis) follow up: mean 30 days</strong></td>
<td>1431 (13 RCTs)</td>
<td>VERY LOW d,e,f</td>
<td>RR 0.97 (0.73 to 1.30)</td>
<td>112 per 1,000 (30 fewer to 34 more)</td>
</tr>
<tr>
<td><strong>0Intensiivravi suremuse vähemine SSC Kumar metaanalüüs/metaregression (septilise šokiga või kriitilise seisundis patsienidid)</strong></td>
<td>(12 observational studies)</td>
<td>LOW c</td>
<td>Suremuse vähemine kombinatsiooniravigrupis patienidel, kel suremuse risk &gt;25% (OR 0,51) (0,36-0,72).</td>
<td></td>
</tr>
<tr>
<td><strong>28-päeva suremuse vähemine SSC Kumar tõenäosusõpühine sobitamisansalüüs (septilise šokiga patsiendid)</strong></td>
<td>2446 (1 observational study)</td>
<td>VERY LOW c</td>
<td>HR 0.77 (0.67 to 0.88)</td>
<td>363 per 1,000 (102 fewer to 35 fewer)</td>
</tr>
<tr>
<td><strong>7, 15 ja 30 päeva suremuse vähemine Ripa tõenäosusõpühine sobitamisansalüüs (septilise šokiga patsiendid)</strong></td>
<td>(1 observational study)</td>
<td>LOW c</td>
<td>Suremuses ei esinenud statistiliselt olulist erinevust kombinatsiooniravi- ja monoterapiaigrupi vahel: 7 päeva (OR 1,04; 0,36–3,02), 15 päeva (OR 0,93; 0,35–2,45) ja 30 päeva (OR 1,23; 0,48–3,12). Neutropeeniliste patienitele (n=69) suremuse oli tõenäoliselt oluliselt väiksem kombinatsioonigrupis 15 päeval (OR 0,29; 0,09–0,92) ja 30 päeval (OR 0,25; 0,08–0,79).</td>
<td></td>
</tr>
<tr>
<td><strong>14-päeva suremuse vähemine Ong (raske sepsisega ja septilise šokiga patsiendid)</strong></td>
<td>648 (1 observational study)</td>
<td>VERY LOW d</td>
<td>OR 1.41 (0,94 to 2,12)</td>
<td>294 per 1,000 (13 fewer to 175 more)</td>
</tr>
<tr>
<td><strong>Intensiivravi suremuse vähemine SSC Kumar metaanalüüs/metaregression (sepsisega või septilise šokiga patsiendid)</strong></td>
<td>(62 observational studies)</td>
<td>VERY LOW c</td>
<td>62 andmetabeli analüüs ei esinenud erinevust suremuses kombinatsiooniravi ja monoterapiaa grupi vahel (OR 0,856; 0,713-1,027). Madala suremuse riskiga patienidel (&lt;15% monoterapiaa grupis) esines statistiliselt oluliselt suurem šanss surra kombinatsiooniravi korral (OR 1,53; 1,16-2,03)</td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; OR: odds ratio; HR: hazard ratio; RCT: randomized controlled trial

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

**Source:** authors’ own compilation.
16.17 Annex 17. When to make a strong recommendation in the face of low or very low certainty of evidence

<table>
<thead>
<tr>
<th>Situation</th>
<th>Condition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>When low-quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high)</td>
<td>Fresh frozen plasma or vitamin K in a patient receiving warfarin with elevated INR and an intracranial bleed. Only low-quality evidence supports the benefits of limiting the extent of the bleeding</td>
</tr>
<tr>
<td>2</td>
<td>When low-quality evidence suggests benefit and high-quality evidence suggests harm or a very high cost</td>
<td>Head-to-toe CT/MRI screening for cancer. Low-quality evidence of benefit of early detection but high-quality evidence of possible harm and/or high cost (strong recommendation against this strategy)</td>
</tr>
<tr>
<td>3</td>
<td>When low-quality evidence suggests equivalence of two alternatives, but high-quality evidence of less harm for one of the competing alternatives</td>
<td><em>Helicobacter pylori</em> eradication in patients with early-stage gastric MALT lymphoma with <em>H. pylori</em> positive. Low-quality evidence suggests that initial <em>H. pylori</em> eradication results in similar rates of complete response in comparison with the alternatives of radiation therapy or gastrectomy; high-quality evidence suggests less harm/morbidity</td>
</tr>
<tr>
<td>4</td>
<td>When high-quality evidence suggests equivalence of two alternatives and low-quality evidence suggests harm in one alternative</td>
<td>Hypertension in women planning conception and in pregnancy. Strong recommendations for labetalol and nifedipine and strong recommendations against ACE inhibitors and ARBs – all agents have high-quality evidence of equivalent beneficial outcomes, with low-quality evidence for greater adverse effects with ACE inhibitors and ARBs</td>
</tr>
<tr>
<td>5</td>
<td>When high-quality evidence suggests modest benefits and low-/very low-quality evidence suggests possibility of catastrophic harm</td>
<td>Testosterone in males with or at risk of prostate cancer. High-quality evidence for moderate benefits of testosterone treatment in men with symptomatic androgen deficiency to improve bone mineral density and muscle strength. Low-quality evidence for harm in patients with or at risk of prostate cancer</td>
</tr>
</tbody>
</table>

Notes. INR: international normalized ratio; CT: computerized tomography; MRI: magnetic resonance imaging; MALT: mucosa-associated lymphoid tissue; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

*Source:* Neumann et al. (2016).

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Reprinted from *Journal of Clinical Epidemiology,* 72, Neumann I, et al. A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach, 11, Copyright 2020, with permission from Elsevier.
### 16.18 Annex 18. Examples of recommendations formulated in Estonian

<table>
<thead>
<tr>
<th>Tugev soovitus teha</th>
<th>Sõnastuse näited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kui kahtlustate patsiendi kõrgvererõhktõbe, <strong>hinnake</strong> alati tema üldist südame-veresoonkonna haiguste riski. Kõiki alkoholitarvitamise häire kahtlusega täiskasvanuid patsiente <strong>sõeluge</strong> AUDITi testiga esmatasandi tervehoiuis. Patsiendi ohutuse tagamiseks <strong>käsitage</strong> kõikides operatsioonitubades struktureeritud kirurgilise ohutuse kontrollkaarti. <strong>Tõstke</strong> lamavatel patsientidel surve vähendamiseks kandu. <strong>Kasutage</strong> eale ja kognitiivsele võimekusele vastavat valideeritud valuskaalat. <strong>Manustage</strong> valuvaigistavaid ravimeid võimalusel suukaudselt. Ägeda hingamisteede infektsiooni koral <strong>määra</strong> antibakteriaalne ravi astmahaigele ainult juhul, kui tegemist on bakteriaalse infektsiooniga.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nõrk (tingimuslik) soovitus teha</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vajadusel sõeluge</strong> alkoholitarvitamise häire kahtlusega patsiente AUDIT või AUDIT-C testiga eriarstiabisis. <strong>Kaaluge</strong> kaks aastat pärast operatsiooni luutiheduse uuringu tegemist. Kontrollimatu söömiskäitumisega patsiendile <strong>soovitage</strong> kognitiiv-käitumuslikke ravimeetodeid. <strong>Määra</strong> lamatisega patsiendile peale tavatoidu lisatoitu <strong>vaid juhul</strong>, kui patsiendil on tuvastatud puudujääg senises toitumises.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Hea tava suunis või praktiline soovitus</td>
<td>Ravijuhand sisaldab suuniseid, mis põhinevad ravijuhandi töörühma liikmete kliinilisel kogemusel, ja mis võivad olla praktikas abiks parima ravitulemuse saamisel.</td>
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</tbody>
</table>
### 16.19 Annex 19. Model form for the guideline implementation plan

<table>
<thead>
<tr>
<th><strong>Data</strong></th>
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<tbody>
<tr>
<td><strong>Objective</strong></td>
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<td><strong>Barriers</strong></td>
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<td><strong>Main success factors</strong></td>
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<td><strong>Resources or preconditions required for implementation</strong></td>
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<td>Activities or considerations related to the implementation plan</td>
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<tr>
<td><strong>Dissemination</strong></td>
</tr>
<tr>
<td><strong>Provision of the clinical guideline to stakeholders</strong></td>
</tr>
<tr>
<td><strong>Media coverage</strong></td>
</tr>
</tbody>
</table>
| **Education and training** | The following should be briefly described:  
- educational events (conferences, workshops, continuing education);  
- topics of planned courses (lectures, seminars, videos);  
- list of leading trainers (for developing teaching aids: slides, handouts, trainer handbook, case descriptions, basic test for learners, a summary of content and length of videos); usually this comprises 4–6 members of the Guideline Unit and Panel. | |
| **Monitoring** | A list should be compiled to outline the expected process, outcomes and evaluation dates, including:  
- a description of the indicators and objectives of the audit;  
- measurement of the reference level of indicators (unless described in the topic proposal). | |
| **Integration into the computerized decision-making support system** | It should be ensured that the recommendations can be implemented and integrated into the computerized decision-making support system. | |