World Health Organization
REGIONAL OFFICE FOR Europe

Options for best practice clinical guideline development in Ukraine

Policy brief

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Abstract

The Ministry of Health of Ukraine requested support from WHO for the process of standardizing health care and strategic purchasing of services by guiding the development of evidence-based clinical guidelines in line with best practices and the country context. From October 2020 to February 2021 WHO conducted a preliminary study to assess the options the Ministry should consider for implementing the national clinical guideline development process. This policy brief was developed to summarize the findings of the study and describe best practices, processes and methods for developing guidelines in Ukraine. The study found clear evidence of general support for the process of revising clinical guidelines, moving away from simple translation to a more structured process of systematic adaptation of guidelines. Key messages include the requirement for investment in capacity development for skills and competencies and the need to develop a process for the system for transparent management of conflicts of interest.

Keywords

QUALITY OF HEALTH CARE
EVIDENCE-BASED MEDICINE
UKRAINE

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Contents

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Internal review of the draft publication was provided by Elina Dale (Health Policy Adviser, WHO Country Office in Ukraine) and Svitlana Pakhnutova (Medicines Policies Officer, WHO Country Office in Ukraine).

Leading technical consultations were provided by Jarno Habicht (WHO Representative and Head of Country Office in Ukraine), John Grove (Director, Quality Assurance of Norms and Standards, WHO headquarters) and Kidist Kebede Bartolomeos (Unit Head, Quality Assurance of Norms and Standards, WHO headquarters).

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Abbreviations

CPD	continuing professional development
EBM	evidence-based medicine
EML	essential medicines list
EU	European Union
GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	health technology assessment
IT	information technology
NHSU	National Health Service of Ukraine
NICE	National Institute for Health and Clinical Excellence (United Kingdom)
SDG	Sustainable Development Goal
TB	tuberculosis
UHC	universal health coverage

Executive summary

Standardization of care through the introduction of clinical practice guidelines is a high priority for Ukraine, as noted on several occasions by the leadership of the Ministry of Health. Recognizing its importance, the Ministry issued Order 590 in February 2020. This articulates the need to develop standards of practice to support both improved quality of care and strategic purchasing of services. The Ministry requested support from WHO in this process to guide clinical guideline and protocol development, in line with best practices and the country context, with the goal of ensuring that patients in Ukraine receive safe, high-quality care.

From October 2020 to February 2021 WHO undertook a scoping study to assess the options the Ministry of Health should consider for implementing a national clinical guideline development process. The various legal orders enacted since 2012 were reviewed, together with the report of a major project on clinical guideline development in Ukraine carried out in 2004–2006. Representatives from key organizations were interviewed about their views on how best to implement a revised national guideline system. The draft order on clinical guideline development was also assessed, and comments were provided to the Ministry. As part of the process, WHO also conducted three webinars with interested stakeholders, including one on current international standards for clinical guideline development processes. This policy brief summarizes the results of this study and describes best practice structures, processes and methods for guideline development in Ukraine.

The study found clear evidence that there is general support for a revised clinical guideline process, moving away from simple translation to a more structured process of systematic adaptation of refence guidelines from other countries. Management of conflicts of interest needs to be addressed as a priority to ensure that guideline recommendations are robust and acceptable to all.

Establishing a system will require investment in both staff and capacity. Unless clinical guidelines are developed from the outset alongside plans for implementation, they will be ineffective and a waste of resources. Implementation plans need to include:

- ensuring that the guideline is designed in a way that is appropriate for the end user;
- a dissemination strategy so that the guidelines reach the target audience;
- an education plan so that end users know what the guidelines recommend;
- identification of indicators to show that the guideline recommendations have been adopted;
- a plan for measurement of the indicators and a method for providing feedback about this to end users; and
- a process for ensuring that the guidelines are reviewed and updated in a timely manner.

Key messages

- Clinical guidelines will be most effective when they are regarded as trustworthy, evidence-based, credible and unbiased.
- A systematic approach should be used in development of all guidelines, based on adaptation of quality-assured reference guidelines. Ukraine has recognized this and needs to develop a system to achieve it. WHO can support development of this system.
- Investment in capacity development for skills and competencies is needed. Existing health technology assessment capacity is a good start, but capacity is needed among all stakeholders for guideline development.
- A simple, robust structure is needed to ensure that the guideline system will work.
- A committee with a secretariat based in the Ministry of Health would be the simplest option. The committee should report directly to the responsible Minister, not through the Ministry of Health.
- The system should have a process for transparent management of conflicts of interest, and this needs to be developed as a priority.
- Guidelines are only one tool for improving quality of care: the essential medicines list or "positive list" of medicines, health benefits package, clinical audit and feedback, clinical performance indicators and continuing professional development should all link with guidelines.

1

Introduction and context

Standardization of care through the introduction of clinical practice guidelines is a high priority for Ukraine, as noted on several occasions by the Minister of Health. Recognizing its importance, the Ministry of Health issued Order 590 in February 2020. This articulates the need to develop standards of practice to support strategic purchasing of services and improved quality of care. The Ministry requested support from WHO in this process to guide clinical guideline and protocol development, in line with best practices and the country context, with the goal of ensuring that patients in Ukraine receive safe, high-quality care.

Quality is defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" *(1)*. Quality of care is a key component of the Sustainable Development Goals (SDGs) agenda and, as stated in the WHO *Handbook for national quality policy and strategy (2)*, the SDGs place clear emphasis on achieving universal health coverage (UHC). The *Handbook* further notes that UHC means "ensuring that all people and communities can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship". Quality of care at all levels of a health care system is very difficult to achieve without standardization of care through evidence-based clinical practice guidelines.

This policy brief focuses on the structures, processes and methods for guideline development. Unless clinical guidelines are developed from the outset alongside plans

for implementation, however, the guidelines will be ineffective and a waste of resources. Implementation plans need to include:

- ensuring that the guideline is designed in a way that is appropriate for the end user;
- a dissemination strategy so that the guidelines reach the target audience;
- an education plan so that end users know what the guidelines recommend;
- identification of indicators to show that the guideline recommendations have been adopted;
- a plan for measurement of the indicators and a method for providing feedback about this to end users; and
- a process for ensuring that the guidelines are reviewed and updated in a timely manner.

2

The role of clinical practice guidelines in improving quality of care

The components of quality of care include making sure that health care services are effective, safe and “people-centred” – that is, they respond both to individual clinical needs and to preferences and values. In addition, health care services should be timely, equitable, integrated across levels and providers, and efficient.

Clinical practice guidelines, treatment guidelines, clinical protocols and care pathways are accepted as key tools to improve overall quality of care, reduce variation in clinical practice and reduce the rate of error in medical care. Adherence to clinical practice guidelines by health care workers is likely to result in improved efficiency and cost–effectiveness of care.

Over the past 20 years, standards for clinical guideline development have evolved. Once a process primarily based on expert opinion, they now involve highly structured and systematic approaches to evidence synthesis and development of recommendations to provide clinicians with guidelines that can be easily accessed and applied at the point of care. In some countries formal institutions have been put in place to provide guidelines for all the clinicians in the country (such as the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom); in others the ministry of health sets standards for development of guidelines but leaves it to hospitals or professional associations to develop them.

2.1 Why isn't expert opinion enough?

The dictionary definition of "expert opinion" is a belief or judgement about something given by an expert on the subject. As described by Martin Burton *(3)*, it has become clear over the last three decades that expert opinion alone is insufficient as the basis for decisions in clinical practice *(4)*. The scientific evidence is so extensive that only systematic assessment of evidence quality and systematic appraisal of benefits and harms can produce consistently trustworthy conclusions. Examples are numerous of interventions that were adopted on the basis of expert opinion but were found, when the evidence available at the time was evaluated properly, to have no benefit or to cause harm.

Expert opinion is sometimes considered to be evidence. For example, the Canadian Task Force on the Periodic Health Examination originally considered expert opinion the lowest level of evidence *(5)*; this can still be found in hierarchies of evidence *(6, 7)*. Best practice does not recognize unsupported expert opinion as "evidence", however. To count as evidence, information must be independently verifiable and reproducible. This applies equally to patients and patient representatives, and to health professionals with clinical experience and expertise.

Expert opinion – including that of patients – is, however, needed to interpret systematic reviews of evidence and summary evidence tables, and to contextualize evidence for application in a particular health system. Methods for systematic reviews have become standardized, especially through the work of the Cochrane Collaboration *(8)*, established in 1993 to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesized research evidence.

2.2 High-quality guidelines

The core components for trustworthy guideline development *(9–13)* indicate that guidelines should:

be developed by a knowledgeable, multidisciplinary panel of experts and representatives from affected groups;

- be based on a systematic review of the existing evidence;
- consider important patient subgroups and patient preferences;
- be based on an explicit and transparent process that minimizes distortions, biases and conflicts of interest *(14)*;

- provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations *(15–18)*;
- link the evidence considered and the expert judgements about the evidence to the recommendations transparently *(19–21)*;
- be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

The Guidelines International Network (GIN) has published a standard for clinical practice guidelines. Table 1 lists the components that are considered part of a high-quality guideline. The same components are also set out in the WHO Handbook for Guideline Development *(22)*.

Table 1. Components of a high-quality guideline

Component	Description
Composition of guideline development group	The guideline development panel includes diverse and relevant stakeholders, such as health professionals, methodologists, experts on a topic and patients.
Decision-making process	The guideline describes the process used to reach consensus among the panel members and, if applicable, approval by the sponsoring organization. This process was established before the start of guideline development.
Conflicts of interest (disclosure)	The guideline includes disclosure of the financial and nonfinancial conflicts of interest for members of the guideline development group.
Conflicts of interest (resolution)	The guideline describes how any conflicts identified were recorded and resolved.
Scope of a guideline	The guideline specifies its objective(s) and scope.
Methods	The guideline clearly describes the methods used for guideline development in detail.
Evidence reviews	The guideline uses systematic evidence review methods to identify and evaluate evidence related to the guideline topic.
Guideline recommendations	The guideline recommendations are clearly stated and based on scientific evidence of benefits, harms and – if possible – costs.
Rating of evidence	The guideline uses a rating system to communicate the quality and reliability of the evidence.
Rating of recommendations	The guideline uses a rating system to communicate the quality and reliability of the strength of its recommendations.
Peer review and stakeholder consultations	Review by external stakeholders was conducted before guideline publication.
Guideline expiration and/or updating	The guideline includes an expiry date and/or describes the process that guideline groups will use to update recommendations.
Financial support and sponsoring organization	The guideline discloses financial support for the development of both the evidence review and the guideline recommendations.

Source: adapted from Guidelines International Network *(23)*.

Developing guidelines of acceptable quality is a resource-intensive, time-consuming process, and requires sophisticated methodological expertise. For these reasons, recent interest has been seen in defining acceptably rigorous methods for adapting existing guidelines to different contexts and settings. Some experience has been documented – for example, from Estonia and Kazakhstan. A key question is how best to adapt clinical guidelines from high-income country settings to middle- and low-income country health systems. Several recent studies describe experiences of adapting clinical guidelines from WHO and note the two broad approaches: "copying and customizing" and "capacity-building" *(24–26)*. One important point that arises from the experiences described is that significant capacity is necessary even to copy and customize guidelines. Capacity development is further discussed below.

2.3 How guidelines need to link to other aspects of the health system

To have an impact on quality of care, clinical guidelines need to be synergistic with other "levers" in the health care system that support behaviour change. These include the benefits package (where such a system exists), the "positive list" of essential medicines and health products, the procurement system and a monitoring/quality improvement system aligned with the clinical guideline recommendations *(27, 28)*. There is no point, for example, in a guideline recommending use of an expensive medicine if this is not covered by the benefits package: either the recommendation will not be followed, or patients will have to pay the cost out of pocket. For alignment of all the levers to occur, the various organizations involved in health care delivery need to agree on the criteria for making guideline recommendations, especially in resource-constrained settings.

Improving quality of care can be reinforced by additional strategies, such as systematic support of behaviour change targeting health care workers (for example, academic detailing, or audit and feedback using routinely collected prescription or clinical data), pay-for-performance schemes and requirements for continuing professional development (CPD) or recertification.

3

Systems and methods for guideline development

3.1 Systems

The national systems for guideline development in the European Union (EU) were described in 2012 *(29)*. As the premise underpinning the use of clinical guidelines is that they facilitate the effective translation of evidence into clinical practice, it is important to make clear that a prerequisite for clinical guidelines being effective is a culture of evidence-based medicine (EBM). This needs to be developed over time through appropriate medical and health workforce education. Stakeholder engagement is essential through any guideline process, and this needs to be built into the system and process from the start.

The components of a system for developing clinical guidelines are:

- a regulatory or legal framework;
- a designated authority to prioritize topics, oversee development and quality assurance of guidelines, and oversee capacity development;
- a budget sufficient to support the activity of the designated authority, to pay members of the guideline development groups for their work, and to pay for capacity development;
- a systematic and transparent process of guideline development, based on an agreed handbook of methods and criteria for decisions, using current information technology (IT) platforms as appropriate;

- a systematic approach to dissemination and implementation, with responsibilities assigned to stakeholders;
- methods for evaluation of the guidelines, including measuring performance with agreed clinical indicators and for updating guidelines as needed;
- specification of links with medicines and health technologies regulatory agencies and procurement systems.

3.1.1 Regulatory/legislative basis

Not all countries with a long history of use of clinical guidelines have a formal legal structure that supports their process (as the United Kingdom does, for example). The legal standing of guidelines varies: in some countries (such as Italy) compliance with parts of guidelines is mandatory; in others there is no requirement to comply. There is also considerable variation in the level at which guidelines in EU countries are developed: some countries have centralized quasi-governmental organizations responsible for guideline development, while others use a decentralized approach that relies more on regional structures or professional societies.

Issues to consider when deciding on the regulatory and legal framework include the legislative structures that support the health care system generally (whether most doctors are state employees or self-employed), the culture in the clinical community (whether it is reliant on experts or more evidence-based), the mechanisms for procurement of health care services and health products (whether the state controls pharmaceutical imports) and the system of payments.

3.1.2 A designated authority to prioritize topics, oversee development and provide quality assurance

Considerable variation also exists in approaches to selecting and prioritizing guideline development. Some countries rely on a centralized priority-setting process, often run by the ministry of health, whereas others leave it entirely to professional societies to develop guidelines as they choose, and some countries apply a blend of these approaches. While there is no single "best" approach, allowing a high degree of freedom of choice risks duplication and wasted resources, inadequate guideline development for key areas and inadequate coordination with authorities controlling other parts of the health care system. For this reason, when a system is being set up for the first time, it is recommended that there should be a designated central authority. This can be a small committee with appropriate representatives – the guideline advisory board in Estonia is an example. It is important that this authority or designated structure should have responsibility and authority for establishing the quality assurance process used

in the guideline development process, as well as overseeing the timely completion of guidelines. It should also have responsibility for ensuring that appropriate capacity development is undertaken.

3.1.3 Budget

Most systems of guideline development that are sustained over a long period rely on financial support to at least key personnel. The size of the organization can range from that of NICE, with several hundred staff paid as full-time employees plus contractual arrangements with academic centres, to a small secretariat of perhaps 10 staff in a ministry of health. To reduce the risk of potential conflicts of interest, paying guideline group experts for the time they contribute to a guideline will mean that they are less likely to seek other financial support – for example, from the pharmaceutical industry. A budget allocation should therefore be dedicated to guideline development, through the designated authority.

3.1.4 A defined process

The key principle is to have a national handbook that is publicly available and sets out agreed and approved methods for guideline development with minimum requirements. Methods for guideline development have evolved significantly over the past two decades. Countries in the EU use different approaches, but to ensure quality and consistency many countries adopt a standardized approach at a national level.

The minimum requirements for a handbook are that it specifies a transparent process with strategies to manage conflicts of interest (see section 6) and describes how guideline development groups are to be selected, who can be involved, and how the group is to use evidence in decision-making (including any decision criteria that are to be used). The handbook should also describe how the guidelines are to be disseminated, specify methods for selecting clinical indicators to be used in performance appraisal, and provide direction on how and when to update guidelines. A number of IT platforms can now be used to support guideline development. More details on options for methods are described below (section 3.2).

3.1.5 Dissemination and implementation

Guidelines will not be useful if dissemination and implementation are not included as an integral part of guideline planning and development. Electronic options for dissemination are now common, whether through decision support systems, mobile phone applications or other IT structures that are part of the health care system.

Dissemination strategies should be linked with educational programmes, including through CPD for health care workers.

A systematic implementation strategy is required in general, but also for specific guidelines. Most countries do not have legally binding guidelines for all conditions. In the EU mandatory clinical guidelines and protocols are applied only to special cases, such as notification requirements for occupational health conditions and infectious diseases. Other implementation strategies include financial incentives such as pay for performance, education using approaches such as academic detailing, and audit and feedback. A few countries have organizations specifically responsible for implementation of guidelines, such as NICE in the United Kingdom and Australia's National Prescribing Service *(30)*.

3.1.6 Methods for evaluation and updating of guidelines

Evaluation of the impact of guidelines on clinical care and health outcomes is challenging, and few countries do it systematically. If guidelines specify clinical indicators that can be measured through routine data collection, however, these items can be used to assess change in behaviour and possibly health outcomes over time. If a health insurance system collects prescription data, the information can be used to assess prescribing behaviour. Similarly, pathology test ordering and radiology test ordering can be assessed in relation to specific guidelines. Other means of evaluating guidelines can include assessing health care workers' knowledge of specific guidelines, although this may not very readily translate to improvements in health outcomes. It may be helpful to establish a specific academic group or centre with expertise in evaluation methods as part of a guideline system.

3.1.7 Links with other components of the health system

For guidelines to be effective, the recommendations should align with other legal and administrative instruments that exist in a health system. For example, if a country has a positive list of medicines that are reimbursed by the health insurance system, there should be consistency between the medicines included in the list and those recommended in the guidelines, as well as a process for resolving discrepancies. Similarly, guideline recommendations about delivery of services should be consistent with activities that can be carried out by different types of health care workers – for example, if nurses are not allowed to give injections, there is no point in having a recommendation for midwives to give injectable oxytocin in maternal care.

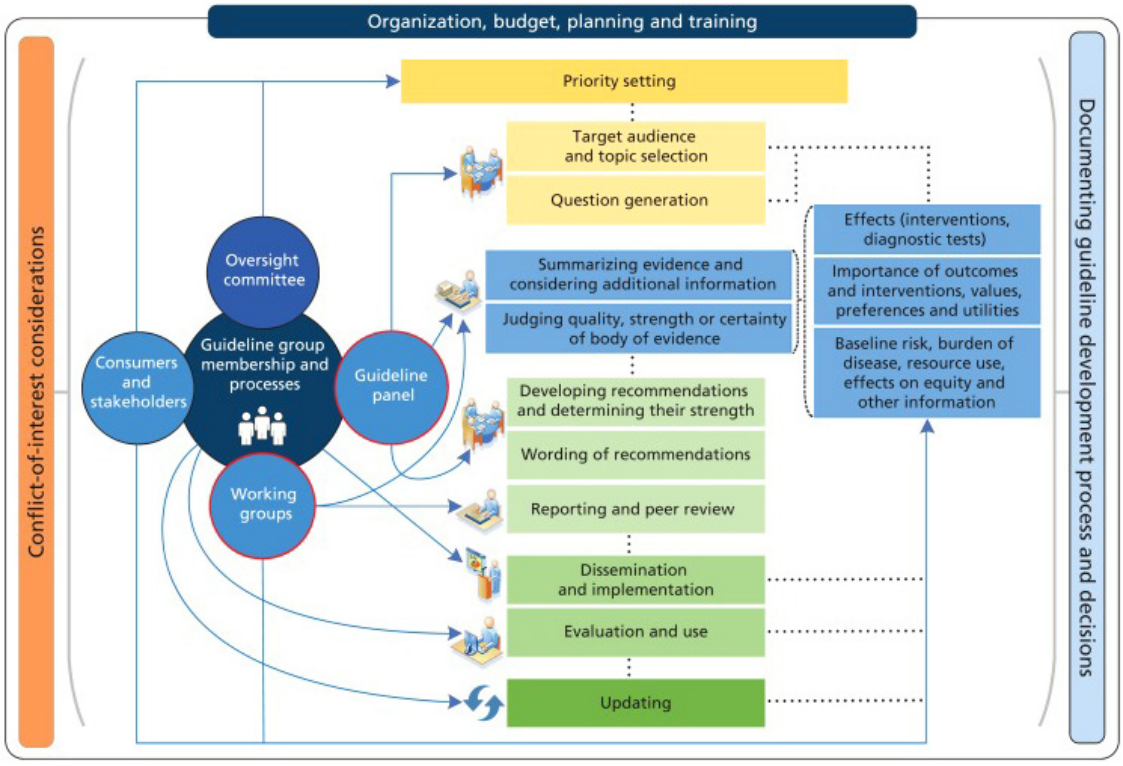
It is important to have a clear "hierarchy" for resolving these decisions, depending on the system of decision-making used for the different instruments. In England and

Wales, once NICE has made a positive recommendation, procurement of the service or product is undertaken by the local authority. In Australia, on the other hand, use of medicines and diagnostic tests in primary care is determined by their listing on positive lists (the Pharmaceutical Benefits Schedule and Medicare Benefits Schedule), rather than guideline recommendations. The need to resolve inconsistencies and contradictions across the health care system is an important reason the guideline development authority should have direct access to the highest level of government authority.

3.2 Processes and methods for guideline development

The methods for guideline development have become standardized, as shown in summary in Fig. 1.

Fig. 1. The guideline development process



Source: Schunemann et al. *(11)*.

The aspects of the process summarized in Fig. 1 that are most important for readers of this policy brief are:

- stakeholder engagement;
- *de novo* ("from scratch") guideline development versus adaptation or adoption;
- a handbook of agreed methods and processes.

3.2.1 Stakeholder engagement

Stakeholder engagement is a necessary component of guideline development and implementation, and can help to ensure a guideline's feasibility and acceptability for end users. Engagement of appropriate stakeholders will also ensure that equity and human rights issues are taken into consideration, and support the incorporation of guideline recommendations into broader policy and practice. Nevertheless, while many stakeholder groups are affected by recommendations in guidelines – including patients, consumers, providers, the general public, researchers, industry and policy-makers – no global consensus is yet in place on how best involve all groups, although an extension of the GIN/McMaster checklist describing best practice and approaches to stakeholder involvement is in development *(31)*. The broad principle is that little may be lost by including a wide range of stakeholders in the consultation process, but a great deal may be lost by failing to consult an important stakeholder.

Based on experience in national systems of guideline development, the following issues need to be considered and documented in a handbook of methods:

- who should be considered the stakeholders in a specific guideline under development, and why;
- what their input will be and how their conflicts of interest will be managed;
- how the process will be documented transparently.

Another factor that needs to be addressed is the availability and acceptability of different methods of stakeholder engagement – for example, electronic or written input, or face-to-face meetings – as well as the resources required and available to ensure meaningful input. It should be recognized that some stakeholders, such as patient groups, may not have the resources to provide useful input, especially if written submissions are required or a number of guidelines are being developed simultaneously in their area of interest. Support may need to be provided by the designated authority – the government – to allow poorly resourced stakeholders to have an effective voice while avoiding the risk of their resorting to funding from sources that raise issues of conflict of interest, such as the pharmaceutical industry.

3.2.2 De novo guideline development versus adaptation

De novo guideline development is complicated, resource and time intensive and requires a high level of expertise – an 18-point checklist has been published *(11)*. Guidelines developed according to these standards require financial and human resources and, given the large number of guideline development organizations now active around the world, the risk of duplication of effort and wasted resources is significant.

Particularly in low- and middle-income countries, options other than developing guidelines *de novo* should be considered. There are few areas of medicine where it is not possible to find a recent, high-quality guideline from a national authority or international specialist society. WHO and GIN have an extensive catalogue of clinical guidelines on specialized topics of particular public health importance, including tuberculosis (TB), HIV and maternal health.

Several frameworks for systematic approaches to adaptation of "reference" guidelines have been published and tested (such as the ADAPTE and GRADE-ADOLOPMENT frameworks) *(25, 32–34)*. In countries with limited resources it is more appropriate to use one of these systematic adaptation approaches as it will be cheaper and faster, and is likely to produce guidelines of better quality. There should be agreement on how recommendations will be reviewed, what kind of adaptation of the recommendation is necessary and how this will be done transparently and fairly. Further resources and approaches on how to adapt reference guidelines can be found in the Estonian Handbook *(35)* and other resources, such as electronic guideline production and dissemination platforms *(25, 26, 33)*.

3.2.3 A handbook of methods

Given all the complexities and options for guideline development, it is essential to have an agreed approach to it for a given setting *(36)*. The most effective way to do this is to prepare and publish a document that describes all the methodological and process issues outlined above. This document can be used as the basis for handbook development at a national level; it is also integrated in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline development tool *(11, 37, 38)*. Annex 1 contains a glossary providing further details and links to resources.

4

The current situation in Ukraine

4.1 Structures and organizations

The principal instruments for ensuring delivery and quality of care in the health care system are legislative orders issued by the Ministry of Health. Fig. 2 illustrates the various stakeholders involved in the health care system who may be relevant to clinical guideline development.

Fig. 2. Influences on clinical practice in Ukraine

As of September 2020, the Ministry of Health has 10 directorates: Strategic Planning and Coordination, International Cooperation and European Integration, Public Health and Disease Prevention, Supply of Medical Care, Quality of Life, Medical Personnel, Education and Science, Financial and Economic, Pharmaceutical Supply, Advanced Medical Care, and Innovations and Development of Digital Health Transformations. Each is responsible to a Deputy Minister and ultimately to the Cabinet of Ministers, the Prime Minister and the President. The legislative organs monitor the health system through the Parliamentary Health Committee.

In 2018 the National Health Service of Ukraine (NHSU) was created as the strategic purchasing agency and driver of Ukraine's move towards UHC. This is a new and emerging institution, which currently has 300 staff and is growing fast. The NHSU workforce – including departments in the regions – has been capped at 1060, however, so its ability to play a central role in areas such as guideline development may be limited.

Two other key institutions of the Ministry of Health are the State Expert Centre and the Public Health Centre. The State Expert Centre is a regulatory authority in the area of preclinical research, clinical trials and registration of medicines. It also has a relatively new department carrying out health technology assessment (HTA). The Public Health Centre oversees policy development and implementation of strategies for laboratories, antimicrobial resistance, and infectious diseases and vaccines; it also plays a role in training and capacity-building. The Public Health Centre has been the main recipient of the grant from the Global Fund to Fight AIDS, Tuberculosis and Malaria, and monitors national programmes for HIV and TB.

According to the head of the State Expert Centre, approximately 500 clinical trials are carried out in Ukraine per year, including Phase 1 clinical trials. There is apparently no national ethics body, and at present there is no equivalent of a national medical research council or national public sector research funding organization. Ethics approval may be carried out at the institutional level, but there are no mandatory national guidelines for research ethics. Mandatory national guidelines for research ethics are desirable to help applicants preparing proposals and as a check on arbitrary or biased decision-making.

Outside the ministry structures, the key groups of stakeholders that need to be considered are the Academies of Sciences and Medicine, medical and pharmacy societies and associations, universities and academic institutions, and patient organizations. These commonly draw their support from international foundations and bilateral institutions, but some also may receive private funding – including from pharmaceutical companies – thereby creating issues related to conflict of interest.

An important issue is whether pharmaceutical and medical device manufacturers are to be considered stakeholders. A desirable central principle is that if they are consulted

as stakeholders in a particular case or in general, the process of consultation must be transparent and limited to areas where consultation may advance a public interest that has been specified in advance (such as increasing local manufacturing capacity).

Procurement for centralized governmental programmes is currently handled by the Central Procurement Agency of the Ministry of Health, state-owned enterprise Medical Procurement of Ukraine and international agencies (United Nations Development Programme, United Nations Children's Fund and Crown Agents). Lists of what is needed are provided by 38 vertical programmes.

4.2 Previous strategies for promoting quality of care and clinical guidelines

At least three strategies to develop clinical protocols and guidelines have been used in Ukraine over the last 20 years. The initial approach was a clinical guideline development system, overseen by the State Expert Centre with the Ministry of Health. Clinical experts were convened into working groups and tasked to produce guidelines on specific topics. As far as can be determined, no standardized process for guideline development was put in place, and clinicians contributed their time as volunteers. As is often the case with relatively unstructured processes, the guidelines took a long time to produce and were of variable quality.

In 2004–2006 the joint TACIS project was undertaken with the EU to evaluate the guideline system and propose options for Ukraine. The full report of that project was published in 2007 *(39)* and contained detailed recommendations that were consistent with best practice in guideline development at that time. In 2012 the Ministry of Health issued Order 751 on the creation and implementation of medical and technological documents for standardization of medical care in the system of the Ministry of Health of Ukraine, which incorporated most of the recommendations of the TACIS project.

Over the next four years, some guidelines were developed in accordance with the 2012 Order, but very few areas were covered by these guidelines. There were also concerns about the methods used to develop some of them – in particular, whether there was appropriate management of conflicts of interest. In 2016 the Ministry of Health issued Order 1422, which required changes to the methodology of development and implementation of medical standards (unified clinical protocols) for medical care and allowed only translations of a list of reference guidelines from other countries. These sources included, for example, the Finnish DuoDecim guidelines for use in primary care, which are comprehensive and created for a system perceived to have many similarities with Ukraine's. Hospitals and clinicians were provided with a list of

acceptable international sources, including the United Kingdom's NICE guidelines and the United States-based commercial publication *UptoDate*, but were not provided with access to those that required subscription fees. How the translation and the adaptation process was done was left to each hospital to determine. Not surprisingly, this has not been found satisfactory, and it was particularly a problem for choices of medicines and health products, especially with the changes to the financing system introduced in 2017.

With the establishment of the NHSU, the interest in and need for updated and curated national clinical guidelines/protocols became clear. There is also a need to establish a positive list of medicines to be provided as part of the benefits package that is being developed. Ukraine has a national essential medicines list (EML) that guides public procurement and may be the basis for a positive list, but clarification is needed of the processes for updating and maintaining the EML.

HTA processes have been established in Ukraine over the past two years, with the aim of creating a fully independent agency. Decree 1300 of the Cabinet of Ministers on approval of the state HTA procedure, approved in December 2020, mandates state HTA for medicines included in the lists used for public procurement. What is not yet clear is how these retrospective assessments will feed back to decision-making about listing products for procurement, or how they would interact with guideline development.

4.3 Stakeholder opinion survey, November–December 2020

4.3.1 Introduction

As the first step in the WHO scoping study that preceded development of this policy brief, organizations with a stake in the development and implementation of guidelines were identified. Representatives of the organizations were invited to be interviewed about how clinical guidelines were being or ought to be used in Ukraine. Individuals were interviewed in their organizational capacity.

A total of 26 interviews were conducted with 25 individuals, of whom:

- six were officials of the Ministry of Health;
- seven were senior members of the academic staff of medical schools;
- seven were senior members of the medical staff at major specialized medical institutes;
- two were leaders of medical professional associations;
- one was a leader of a patient organization;

- one was a senior staff member of a nongovernmental organization providing health care in Ukraine;
- one was a medical consultant for a pharmaceutical manufacturer.

It should be noted that no health care workers in primary care, in secondary care in non-metropolitan centres or in junior positions were interviewed.

4.3.2 Key themes arising from the interviews

Agreement was nearly unanimous that clinical guidelines are an essential element of a high-performing medical system. The reasons given were that guidelines:

- improve the quality of care;
- give patients confidence that their treatment is appropriate;
- allow doctors to defend their practice; and
- facilitate planning of financial, equipment and staff resources.

Agreement was also nearly unanimous that, to have these benefits, guidelines must be:

- national;
- mandatory;
- evidence-based;
- consistent with the consensus of professional practice within Ukraine; and
- linked to quality indicators so that performance can be assessed.

With regard to the mandatory nature of guidelines, most informants believed that the guidelines should not be rigidly prescriptive, but that clinicians should be able to deviate from them to deal with an individual patient's needs. In practice, the need to adapt guidelines to individual needs can be accommodated flexibly, simply by ensuring that the performance targets linked to guideline implementation do not require that 100% of patients are treated in accordance with the guideline. (The percentage target considered reasonable will vary from case to case.)

The situation prevailing since 2016 was regarded as unsatisfactory at best, and unacceptable at worst. The following quotations are taken from interviewees' responses.

> *It is important for us to develop a single unified medical standard, according to which the NHSU will perform calculations. Today, I have no idea what the NHSU was guided by when it developed the content and accordingly estimated the financial costs for the treatment of those [illnesses] that were included in the state-guaranteed package.*

Since 2016 … all the work with protocols has become so confusing. For example, in the area of stroke treatment, two guidelines – Canadian and Norwegian – can be applied at the same time. This is wrong. There should be a unified protocol for the whole country.

I support the development of unified clinical protocols. This is important for the standardization of medical care – it is important for the doctor, as it protects his professional choice of method of treatment, and is a guarantee of high-quality care for the patient.

Clinical guidelines should be mandatory because:

- *they prevent medical mistakes;*
- *they protect a patient from insufficient competence of the doctor;*
- *they protect a doctor in case of litigation.*

The clinical guidelines should be the benchmark of medical care. … Today we have situations when in the regions the old clinical guidelines are still used and they do not want to accept the new international protocols … for example, under the new guidelines, surgery for breast cancer involves sparing plastic surgery and, in most cases, does not require complete removal of the gland. Instead, doctors from regions keep disabling women, completely removing the gland.

The new clinical guidelines introduced by Order 1422 are not being implemented in most cases in local-level medical institutions. No one monitors the implementation of clinical protocols. I have studied the primary medical records in certain medical institutions (I will not name them), and it's a horror.

Under the amendment, which was made in 2016 … all existing clinical guidelines were repealed, and the so-called international clinical guidelines entered into force. In my opinion, the mandatory nature of those international clinical guidelines is quite conditional and unclear. Each hospital translates and implements them independently. … I have not actually had any clinical guidelines since 2016 on the basis of which I could draw conclusions about the appropriateness of medical care in the event of a conflict situation. The so-called "international clinical guidelines" are not legal norms in a proper sense.

It is a guarantee of our rights: unified clinical protocols determine the content and scope of care that should be provided and, accordingly, the patient has a right to demand them.

It was universally accepted that the basis of national guidelines must be adaptation of guidelines developed in other countries. Creating the large number of national guidelines needed to cover even common medical problems *de novo* was considered clearly unfeasible. Translated guidelines had been found unsatisfactory in practice (although this finding should be considered preliminary because of the absence of lower-level medical and other health care workers in the interview sample).

One problematic aspect of guideline implementation noted by some interviewees was that in rapidly changing areas of practice a rigid process of guideline review may create delays that adversely affect patient care. As one interview noted:

> *In the field of TB, clinical guidelines are changing very rapidly. For example, WHO makes so-called key messages about changes in TB treatment, which are eventually included in the WHO clinical guidelines. We receive such key messages from WHO and it would be great if we could make changes to our standards quickly. However, such a "key message" is not a normative document, so we have to wait until all the bureaucratic procedures in WHO are completed and then make changes to our national documents. Sometimes, such a situation can delay public procurement of strategically important drugs for a year.*

To deal with this problem, consideration may need to be given to streamlined guideline processes for highly specialized and rapidly changing fields of practice.

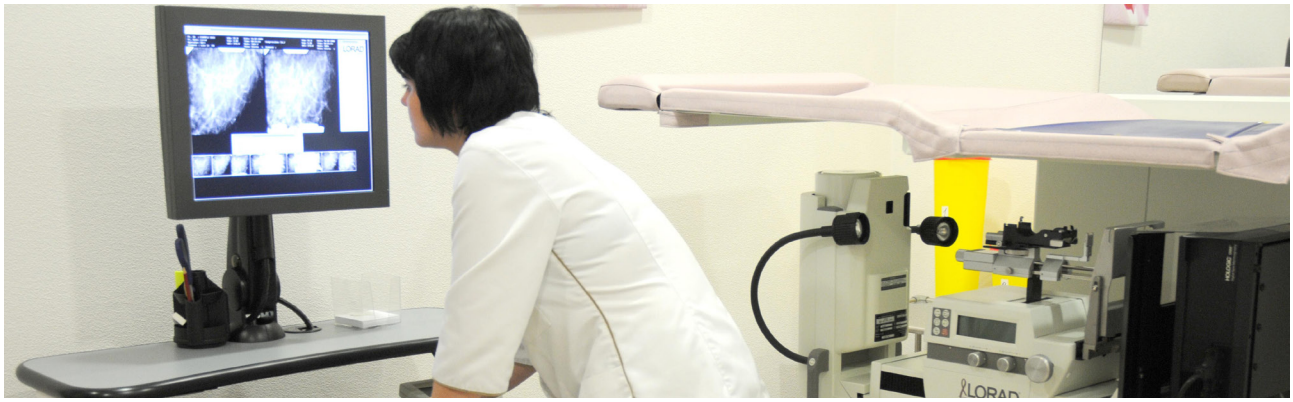
Interviewees expressed concern about the risk of corruption and promotion of sectional professional interests that the adaptation process might offer. They also demonstrated a belief that those risks could be managed, however, and that managing the risk was preferable to the policy of avoiding it by having only translated guidelines.

> *The best option is adaptation. De novo development is very difficult for Ukraine and, to be honest, not necessary. And we know the issue with adoption through translation – again, it doesn't work for the setting.*
>
> *An example of translation is the Ministry of Health of Ukraine clinical guidelines for emergency medical care, which is a copy of the United States guidelines, even with the telephone numbers of American services. It is obvious that such translations are unacceptable and cause rejection in the professional community.*
>
> *The development of clinical guidelines should be funded from the state budget. [It should involve] independent leading specialists who are not in cooperation with the pharmaceutical business and are independent of academic institutions. I believe that the process of clinical guideline development should be observed by independent external experts, such as WHO or international professional associations. If the process is "inhouse" and involves exclusively Ukrainian experts, we will not avoid abuse and lobbying of business or personal interests.*
>
> *Domestic professional associations do not always use evidence-based medicine as a basis: very often they are servants of pharmaceutical manufacturers.*
>
> *It is very important to avoid participation of pharmaceutical lobbyists in the working groups. Conflicts of interest should be avoided when selecting experts for a working group. The working group should include both science representatives and practitioners.*

Patient representatives should also be included, but we have repeatedly observed that representatives of orphan diseases have lobbied for the interests of the pharmaceutical companies, unfortunately.

It is extremely important for our members (patients with different nosologies) to observe the process of clinical protocol development (adaptation) in terms of preventing lobbying of pharmaceutical interests. Today, the process is closed to the patient community, and we are concerned about opportunities for abuse in this area – which is lobbying the business interests of pharmaceutical manufacturers. If we are talking about single-source drugs then everything is transparent, but when it comes to generics or substitute drugs, ensuring transparency of the process is very important.

Interviewees suggested that there is a weakness in national capacity for guideline development, and perhaps even for large-scale adaptation, with regard to understanding of the technical aspects of EBM. This finding needs to be confirmed by discussion with a wider range of informants, especially in the medical universities. If the suggested shortfall in national capacity in EBM is confirmed, this would make it challenging to apply a systematic process of guideline adaptation universally, such as that now recommended by GRADE-ADOLOPMENT *(31)*.



5

Options for guideline development for Ukraine

5.1 Contextual issues to consider for a clinical guideline system

The health workforce in Ukraine is in transition. Currently, 14 public and five private medical schools provide a six-year training programme and produce approximately 13 000 graduates per year. Postgraduate training is generally 1–3 years in total for each specialty. Diplomas are generally not recognized internationally without further training or retraining. The approach used to ensure adequate training is currently a standardized national examination at year 3 and year 6, rather than regulation of medical school curricula. CPD requirements are being introduced, based on a "points for activities" system.

The culture of EBM is not yet well established in Ukraine. Gaps include a lack of clinical epidemiologists as a recognized clinical specialty, lack of training in EBM principles in undergraduate and postgraduate training, and a lack of linkages with key EBM organizations such as the Cochrane Collaboration. These gaps are made more pronounced owing to limited interaction between medical professionals in Ukraine and international standard-setting groups such as professional associations in Europe or the United States. At the same time, there appears to be a group of key opinion leaders in the medical profession in Ukraine who recognize the importance of EBM in

improving quality of care, and who are working on interesting strategies to promote EBM, including through social media.

Sufficient capacity to do what is essential could be developed relatively quickly, with a programme of short-course training in relevant disciplines, including critical appraisal of scientific literature and systematic reviews. In the longer term, a systematic approach to updating medical and public health curricula to include clinical epidemiology will be needed. The competencies needed for guideline development have been described *(40, 41)*, and these skills should also be recognized through the CPD system that is being established.

Health system incentives to provide evidence-based care, including contracting and provider payment methods, are not yet fully aligned in Ukraine, although the basic elements of such structures are in place. These include:

- a national EML;
- state procurement and provision of core essential medicines for the most common medical conditions through the Affordable Medicines Programme;
- establishment of capacity to undertake HTA;
- use of electronic medical records and electronic prescribing payments to primary care providers on a per capita rather than fee-for-service basis; and
- development of benefit packages that include both service and health products.

Patient organizations in Ukraine are also potential supporters of the adoption of evidence-based clinical guidelines and protocols, because widespread adoption of guidelines is a tool to improve both access to health products and overall quality of care. Some of these organizations are part-funded by the pharmaceutical industry (as is common in all countries), which complicates the process of integrating their input into guidelines.

Managing conflicts of interest is a universal challenge. International guideline developers now use various approaches to this issue, however – these mostly rely on transparency and management of declared interests, with strict limitation of input of stakeholder groups such as the pharmaceutical industry. Ukraine could adopt international approaches to this issue; this is discussed further below.

5.2 Options for process

5.2.1 Topic selection

To make the best use of limited resources, topics for guideline development should be prioritized and selected by a designated authority. Appropriate criteria for prioritization include burden of disease, variation in quality of care, availability of evidence that can improve the quality of care, potential impact on efficiency of the health care systems and potential impact on equity. This list is not definitive or exhaustive, and prioritization is an area in which community values and preferences are particularly relevant (see sections 5.2.4 and 5.2.5). The topic selection process should be transparent and should provide opportunities for public input. It should **not**, however, be an application process, as this would bias the system in favour of commercial interests with the resources to produce high-quality applications. Topic selection should be carried out at specified intervals, but with an opportunity for urgent topics to be considered as well *(42, 43)*.

The designated authority could be:

- an independent institution established by the Ministry of Health and reporting directly to the Minister or Deputy Minister;
- a standing committee of experts, appointed by the Ministry of Health and reporting through the chair of the committee to the Minister or Deputy Minister;
- a standing committee of nominated representatives of key organizations plus experts, reporting to the Minister or Deputy Minister.

The designated authority should also have responsibility for overseeing guideline development and making sure that it is in compliance with the national handbook: it must have the authority to reject completed guidelines.

5.2.2 Adaptation

The guideline process in Ukraine should, at least at first, be based on adaptation of specified reference guidelines only. It is suggested that acceptable reference guidelines could be those published by WHO, the Scottish Intercollegiate Guidelines Network *(44)* and specified European specialist societies, along with a limited selection from other national guidelines, within a given date range (for example, within the last three years). Initially, to ensure efficient use of resources, searching for quality-assured guidelines should not be a required part of the guideline adaptation process.

A systematic adaptation process should be used, such as the GRADE-ADOLOPMENT framework. This should be described in the national handbook.

The issue of what to do if no quality-assured reference guideline exists for a specific condition in Ukraine was raised several times in the WHO scoping survey. Given the substantial number of guidelines published internationally, it is highly unlikely that such a situation will occur. The examples given seem to be related to a pattern of clinical practice that is prevalent in Ukraine but not in other countries, or to interest in a particular intervention, with potential conflicts of interest. In the event that no quality-assured reference guideline truly exists, two options could be considered: a collaboration with an international guideline group, or a *de novo* guideline developed in Ukraine according to the full GRADE process. These procedures are so open to inappropriate influence, however, that not allowing any alternative to adaptation of reference guidelines is preferable.

To ensure the most efficient use of resources, a systematic assessment of existing electronic tools for guideline adaptation should be carried out. These include GRADEpro, MAGIC and several others *(37, 45)*.

Once capacity is increased in Ukraine, a shift towards *de novo* or systematic collaborative guideline development might be possible. But this should be considered a lower priority than other aspects of improving quality of care, such as establishing methods for audit and feedback.

5.2.3 Competencies for guideline development

Guideline adaptation and development requires the following expertise: health research methods, clinical trial design, epidemiology and evidence synthesis. A competency model for potential guideline developers has been described *(46)*, but further assessment is needed in Ukraine to determine the current levels of expertise in the areas listed before plans for a competency-based training system can be established. GIN has partnered with McMaster University to develop an online guideline credentialing and certification programme, which approaches competency at four levels: guideline development group member, guideline methodologist, guideline development group chair and guideline instructor *(40)*. While the medical education system is being revised, it may be helpful to consider assessment of current clinicians' knowledge and skills in areas such as clinical epidemiology or critical appraisal as part of CPD activities, to inform decisions about the training needed. A more detailed review of the medical school curricula would also be helpful.

Guideline development groups should not be "elite" groups, with participation restricted to a small cadre of experts – whether in clinical practice or in EBM. It is therefore vital that the training needed for participation in guideline development is offered to the widest possible range of health professionals. It is also important that capacity development

for EBM should not be restricted to health care workers. Patient representatives, in particular, should be included in the skill-development process at the beginning. It is also necessary for Ministry of Health staff and policy-makers who oversee areas such as HTA and guideline development to have the same kinds of skills (although, perhaps, not to the same level). Similarly, employees in the commercial sector should be offered an opportunity to take part in training.

It is critical to avoid access to training becoming a restricted privilege; this also has important implications for **how** training should be delivered. In general, intensive courses lasting 1–2 weeks offer the greatest and most rapid increase in capacity. These are also acceptable from an equity perspective, provided that the training is free of charge (including incidental costs) for participants, and that enough courses can be offered to create a large and diverse pool of potential participants for guideline development groups reasonably quickly. On the other hand, weekly online seminars allow a wider range of participants to benefit than intensive residential courses, but these will not build capacity as quickly.

If it is a high priority to get the guideline development process going rapidly, there will need to be some prioritization of those who can acquire the necessary skills most quickly. This carries a risk of creating a restricted group who have both skills and experience. To avoid this elite group becoming entrenched, the guideline process should ensure turnover by establishing limits on how many guideline development groups individuals can participate in.

5.2.4 Criteria for decisions

The national handbook should specify criteria for decisions – especially criteria for changing the direction of a recommendation from that of the reference guideline. These criteria might include:

- availability (or lack) of medicines in Ukraine;
- patient out-of-pocket costs of a recommendation;
- local health care systems structures; and
- local values and preferences, which are discussed in further detail below.

The umbrella term “values and preferences” refers, in the context of health care guidelines, to two things: judgements about whether some health problems, or some sectors of the population, have a greater claim on resources than others, and judgements about priorities for broader societal values, such as flexible decision-making versus suppression of corruption *(47, 48)*. Most people, in most communities, think that some health problems and some sectors of the population do have a greater

claim on resources – the very young versus the very old, for example, or a condition that is life-threatening versus one that is not life-threatening.

The problem of deciding which health care problems and which sectors of the population have a greater claim on resources is inescapable. A common and plausible solution to this problem begins from the view that the government should use public resources in the most efficient way possible. That is, it should give preference to health problems for which treatment offers the greatest benefit for the lowest cost. If a treatment for a problem already exists, a new, more expensive treatment may not be added to a guideline unless it is much more effective. Where no treatment exists, a threshold level of cost is set, and funding for a new treatment is provided only if its cost is below the threshold.

This approach has the advantage of relative resistance to conflicts of interest because – provided each treatment's cost is publicly disclosed – inclusion in a guideline of a treatment more costly than an existing treatment or above the threshold sets off an alarm. The weakness of this approach is that both considering only the cost of treatment and not the nature of the illness concerned, and using hard thresholds, result in decisions that are widely perceived to be unfair. After all, whether the cost of a treatment is above or below the threshold is largely a matter of luck, and from an individual patient's point of view it is not obvious why whether a necessary treatment is available or not should be determined by luck.

A workable compromise is to replace hard cost thresholds with soft thresholds, above which treatments will not be included in guidelines unless they promote other values. Examples of the values that may be brought into play are a preference for treatments for illnesses affecting children or for life-threatening illnesses, or those that help people especially heavily burdened by illness.

This compromise preserves much (but not all) of the resistance to conflicts of interest that hard thresholds offer. Two caveats should be noted, however. One is that how far non-economic values are allowed to bend the thresholds is a choice that depends on the value placed on resistance to conflicts of interest versus flexibility in decision-making. The second is that the values allowed to bend the cost thresholds must not be developed or applied arbitrarily. The accountability for reasonableness principles provide a test for assessing the values assigned *(49)*:

- the values must be publicly set out before the guidelines development process begins;
- they must be values that all stakeholders can agree are relevant to the decision of whether to include a treatment in a guideline;
- they must apply equally in all cases; and

- there must be a system for detecting and voiding decisions that breach the values guidelines.

5.2.5 Patient and consumer input

A guideline development process should be set up to include representatives of patients and health care consumers for two reasons. The first is that they can contribute as experts, in the same way that statisticians or health economists may be included. For example, a guideline development group will often have to consider questions such as how a particular symptom of illness, or a particular unwanted effect of a medicine, affects work capacity or quality of life; or which of the outcome measures used in a randomized controlled trial is most relevant to patients' everyday lives. These questions should be answered by representatives chosen by patients, both because the answers are more likely to be accurate and because these are the people most affected and they should, as a matter of principle, be allowed to speak on their own behalf. The second reason is that they have a right to be heard as advocates on matters of policy such as resource allocation.

It is important to keep these reasons separate. The people best suited to provide expert input on the everyday reality of living with an illness may not be those best suited to advocate on behalf of patients on matters such as resource allocation. Further, development of the policies and rules under which guideline development groups will operate, and the groups themselves, should be kept separate. Patient advocacy has an important role in the earlier stage, but it is often unhelpful when individual guidelines are being developed. Once guidelines on individual topics are being developed, it is important that patient and health care consumer representatives on guideline groups – like all members – must work within the culture of EBM. Guidelines depend on, for example, randomized controlled trials and systematic reviews as the main source of evidence for guidelines.

Various mechanisms for including patient and consumer input have been used. They include having patients or consumers as members of expert groups, offering opportunities for written comments through web-based processes and having "town hall" meetings and "hearings" of patient groups with the guideline development group. The choice of a particular approach will depend in part on the resources available to support the approach, but whatever mechanism or combination is chosen, it is important to be transparent about what happens as a result of the input from these groups.

To make patient representation effective, the representatives must have the expertise to contribute to discussion and the time to prepare for meetings. That means that patient representatives on a guideline development group must be paid for their time.

It also means that the process of capacity development discussed elsewhere must cover patient representatives.

Whether the advocacy function is accommodated in guideline development groups depends on how and at what stage of guideline development values and preferences influence the guideline choices (see section 5.2.4). The greater the number of values and preferences allowed to influence decision-making in the group, and the wider the latitude the group is given in choosing and applying them, the greater the role for advocacy on behalf of patients in the group. If the guideline development group has little or no flexibility, a patient advocate may not be able to contribute meaningfully to the group's work.

The roles of patient expert and patient advocate are often thought to raise unique issues in relation to potential conflicts of interest, in that their role is taken to be – inherently – a conflict of interest. This is inappropriate. Patient representatives or advocates should not be assumed to be unable or unwilling to make an unbiased assessment of the evidence. On the other hand, they should not be allowed to claim an exemption from the principle that the task of each member of a guideline development group is to make an unbiased assessment of the evidence. That is, the rules concerning conflicts of interest must apply to patient representatives or advocates exactly the same as to all other group members. In particular, no one who is – personally or through the organization they represent – receiving funding, in cash or kind, from a commercial entity with an interest in the guideline may take any part in the guideline development group.

Having a particular illness, or being an advocate for people with an illness, can affect the ability to make unbiased assessment of evidence about it, so all patient representatives have a potential conflict of interest for this reason. For example, a person with breast cancer may rate evidence related to that disease more highly than evidence related to, for example, colon cancer. This potential conflict of interest is more likely to be problematic in groups developing guidelines in broad areas, such as cancer treatment in general, than in groups developing narrowly focused guidelines, such as treatment of breast cancer. In the latter case, declaration of the potential conflict is normally sufficient to mitigate it. In the former case, the group may consider not allowing some members to vote on the final recommendations.

It should be noted that if having the illness concerned in the guideline may be taken to be a conflict of interest, a guideline development process that did not require all members to disclose their personal medical histories would be treating patient representatives unfairly, in that they would be held to a higher standard than other members.

Having a strong pre-existing view on issues relevant to a guideline development group's work also creates a potential conflict of interest, in that the holder of that view may be

relatively resistant to new evidence. A patient advocate or representative should not be assumed to be biased or resistant to new evidence, but the point where advocacy implies a fixed pre-existing view and therefore becomes a conflict of interest is the same as for any other member. If the group judges that a patient representative's views are not based on unbiased assessment of the evidence, that individual should not take part in the group. If it is judged that the representative's views justify a concern that they might be biased, they should be excluded from voting on final recommendations.

6

Managing conflicts of interest

In the context of health guideline development, a conflict of interest arises when a member of the group may have difficulty making an unbiased assessment of evidence because of another interest or role. GIN has published widely agreed-upon principles for the disclosure and management of conflicts of interest, which result from a broad consultation and review of existing policies that are becoming national policies and distinguish between different types of conflicts – for example, financial and nonfinancial *(14, 50, 51)*.

Managing conflicts of interest is essential to ensure credibility and acceptance of the guidelines by avoiding any suspicion that they were not based on unbiased assessment of the evidence. It is therefore critical that possible conflicts of interest are assessed from the perspective of members of the community seeking to assure themselves of the credibility of the guideline development process as a whole. It is important that this is the relevant perspective, because it means that a conflict of interest is relevant to the process if a reasonable person would think that it might have influenced judgement. Therefore, the problem of conflicts of interest cannot be dealt with by observing that no actual bias was observed during the meetings of the guideline development group.

A potentially endless range of interests and roles outside the guideline development process may be perceived as conflicting with the obligation to make an unbiased assessment of evidence. Over-sensitivity to potential conflicts of interest – especially professional conflicts – can paralyse the development process or impair the quality of the guidelines by excluding those with the greatest expertise. Relatively few conflicts (mainly financial) preclude participation in the guideline process, and most professional

and personal conflicts can be managed by limitations such as not allowing members with those conflicts to vote on decisions. The important principle, however, is that the guideline process must be responsible for managing conflicts of interest among guideline development group members. It must never be left to individual guideline group members to decide for themselves whether their conflicting interests are relevant or important. The practical consequences are that the threshold for disclosure of an interest must be very low, and that disclosure of an interest – and assessment of how it should affect the person's participation in the group – must be made before the work of the group begins.

In general, assessment of conflicts of interest among the members of a guideline development group should be done by an independent oversight committee, using rules developed centrally to ensure consistency. Responsibility for management of conflicts of interest in a guideline development process may fall on the guideline chair or observers who assure the impartiality of the process.

Financial conflicts of interest are very likely to be perceived as seriously impairing the credibility of a guideline, and if these are discovered after a guideline is released, public confidence in that guideline and in the guideline process as a whole may be permanently damaged. For that reason, guideline group members must declare any relationship with any entity with an interest in the guideline that has provided, will provide or may provide them a benefit in money, goods or services. Ownership of shares or partnerships in businesses with an interest in the guideline, or interests in patents and other intellectual property – whether by guideline development group members or their immediate family – inevitably creates a conflict of interest. Research grants, consultancies, fees for service on advisory groups and speaking fees – including both cash payment and payment in kind, such as travel or accommodation – received by group members usually create a significant conflict of interest.

Judgement may be needed where a financial conflict of interest may appear to arise from relationships between a guideline development group member's employer – such as a university, patient representative group or nongovernmental organization – and businesses or other entities with an interest in the guideline. In general, there will be a relevant conflict of interest if the financial benefit the employer has received is large, if it was received recently or if possible future benefits are still under negotiation, if there is an ongoing relationship, or if the payment supports activity in areas directly related to the topic of the guideline or the group member's work.

No person who declares any of the conflicts listed, including major institutional conflicts, should serve as the chair of a guideline development group. No person who declares ownership, by themselves or an immediate family member, of shares in a business with

an interest in the guideline or of intellectual property relevant to the guideline should serve in any capacity on a guideline development group. No person who is currently receiving any research grant or other payment – in cash or in kind – from an entity with a commercial interest in the guideline should serve in any capacity on a guideline development group, and any member who accepts any such payment in the course of the group's work must resign from the group.

What role in guideline development can be played by people who have in the past received payments from entities with a commercial interest in the guideline, or who are currently receiving research grants or other payment from entities with noncommercial interests in the guideline (such as patient support or advocacy groups), should be considered on a case-by-case basis. In general, only if the support was minor or a long time ago is full participation in the guideline development group appropriate. In most cases, some limitation of participation is a reasonable compromise, such as participating in discussion but not voting on final recommendations.

Another common source of conflicts of interest is the professional interests of guideline development group members. For example, a researcher who wishes to conduct a controlled trial of a new treatment has an interest in the guideline recommending that it be used only in the context of a clinical trial, and a clinician with special skills in a new treatment has an interest in the guideline recommending it. Some degree of conflict of interest arising from professional roles is universal and inevitable – everyone is, to some degree, biased in favour of what they are most expert in, and no one is equally expert in everything. In most cases, it is sufficient for minor professional conflicts to be declared, except in relation to the chairs of guideline development groups, or where a person is uniquely powerful or authoritative and likely to dominate the group.

The situation where professional activity is most likely to give rise to a significant conflict of interest in a guideline development group is where a person has strongly and persistently advocated for a position on one of the questions the group has to consider. Where the group judges that the person's advocacy is not based on unbiased assessment of the evidence, the person should not take part in the group in any capacity. Where the group judges that the advocacy does not demonstrate bias but could give rise to a suspicion of bias, it may restrict the person's participation – for example, allowing them to take part in discussion but not to vote on final recommendations.

A variant of the conflict that may arise from adopting the role of advocate is where nonprofessional convictions – social, political or religious – predetermine the conclusions an individual will reach on the questions before a guideline development group. The principle is that the place for such convictions to be advanced is when matters of policy are under discussion – that is, when the rules and procedures of the group are being

written. They are, like other conflicts that make it difficult for a group member to make an unbiased assessment of the evidence, out of place in a guideline development group. A person who believes that children should not be immunized under any circumstances, for example, cannot be a member of group developing immunization guidelines.

Personal conflicts of interest arise most often from the circumstance that a guideline development group member, or a member of their immediate family, suffers from the illness the guideline is about. They may also arise from experiences such as being a close observer of a patient's suffering, or identifying intensely with a particular patient group. The distinctive thing about personal conflicts of interest of this type is that their impact depends heavily on the scope of the guideline. The circumstance that a group member has a close relative with lung cancer may be a conflict of interest if the group is developing guidelines on which cancers should have priority in resource allocation, but is probably not if the group is developing guidelines on surgery for lung cancer.

As in the case of professional interests, some degree of bias arising from personal or family interests or experience is inevitable. In the case of personal interests, there is a strong countervailing value of respect for privacy, especially of family members, that argues against wide disclosure. For this reason, most guideline processes confine obligatory disclosure to the guideline development group member's own history, or even make personal conflicts an exception to the rule that group members must not judge the relevance of their conflicts, and allow optional disclosure of personal conflicts. As in the case of professional interests, most cases are adequately addressed simply by disclosure.

7

Conclusion and next steps

Improving quality of care in Ukraine requires evidence-based clinical guidelines. The study found current interest in and political commitment for establishing a process for clinical guidelines that meet the country's needs, and the Ministry of Health has a very ambitious plan to update a huge number of clinical guidelines for priority conditions in a short time. Therefore, a decision-making structure to prioritize guideline topics should be put in place, answering to the highest appropriate level of the government, together with a systematic capacity development programme for skills in EBM. At the same time, a rigorous method of adaptation of reference guidelines through a pilot process should be set up. WHO can support this for guidelines in key clinical areas as prioritized by the Ministry of Health and other key stakeholders. Based on discussions held during the development of the policy brief, cancer, cardiovascular disease and diabetes are proposed as the first areas on which this support should focus..

The approach should include:

- establishing a decision-making structure to prioritize guideline topics that answers to the highest appropriate level of government;
- starting a systematic capacity development programme for skills in EBM; and
- concurrently establishing a rigorous method of adaptation of reference guidelines through a pilot process.

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Annexes

Annex 1.
Guideline development glossary

Algorithm, in this context, is a flowchart or decision-tree to illustrate the choices and recommendations suggested in a clinical practice guideline.

Appraisal of Guidelines for Research and Evaluation (AGREE) instrument is a tool developed through international collaboration that provides a framework for assessing the quality of clinical practice guidelines *(1).*

Assessment of Multiple Systematic Reviews (AMSTAR) checklist is a list of 11 items used to measure the methodological quality of systematic reviews *(2)*.

Budget impact analysis makes clear what the costs and impacts are if a health intervention is implemented on a national scale. For the analysis to be effective, it is important to know – in addition to investments and possible savings at the level of patients, health care providers or practices – how many patients, health care providers and practices are eligible for the implementation strategy. Multiplying these two figures can provide policy-makers with the likely total costs and savings generated by wide distribution of the implementation strategy *(3)*.

Case control studies/case series are studies or a report on a single patient, in which patients who already have a specific condition are compared with people who do not. These often rely on medical records and patient recall for data collection. These types of study are less reliable than randomized controlled trials and cohort studies, because showing a statistical relationship does not mean that one factor necessarily caused the other.

Certainty in test accuracy is certainty in a specified magnitude of sensitivity or specificity (e.g. low, moderate or high accuracy) or certainty that the true sensitivity and specificity lies within their respective confidence intervals.

Certainty in the estimate of effect expresses the certainty in the effect of an intervention considering the body of evidence, and is akin to **certainty of evidence**.

Certainty of evidence is certainty that an estimate of association or effect is correct or, better, that a true effect lies on one side of a specified threshold or within a chosen range. The certainty of evidence – also called confidence in estimates of effects, quality of evidence, strengths of evidence or levels of evidence – is expressed in four categories: high, moderate, low and very low. Categorization depends on an evaluation of the following signalling questions for a body of evidence (the specific domains addressed by scientists are given in quotation marks):

- Are the research studies well done? "Limitations in the detailed study design and execution or also called risk of bias or internal validity"
- Are the results consistent across studies? "Inconsistency"
- How directly do the results relate to the question? "Indirectness, applicability, generalizability, external validity"
- Is the effect size precise – due to random error? "Imprecision"
- Are these all the studies that have been conducted? "Publication bias"
- Is there anything else that makes the results particularly certain? "Large effects, worst case scenario predictors still strong conclusions, exposure-effect relation"

Clinical guideline, clinical practice guideline is a systematically developed evidence-based statements that help providers, recipients and other stakeholders to make informed decisions about appropriate health interventions. Health interventions are defined broadly to include not only clinical procedures but also public health and policy actions.

Clinical question/key question is a question formulated using the population/patient-intervention-comparison-outcome framework, wherein the health care provider asks and answers a series of questions meant to elicit information about the patient and their condition, interventions that have been undertaken or should be taken, any comparisons between the current treatment and possible alternatives, and outcomes to be desired or achieved (see **Population/patient-intervention-comparison-outcome (PICO)**).

Cochrane Collaboration is an international network helping health care providers, policy-makers, patients and their advocates and care-givers make well-informed decisions about human health care by preparing, updating and promoting accessibility to Cochrane reviews to provide "the best evidence for health care"*(4)*.

Cohort studies take a large population and follow patients who have a specific condition or receive a particular treatment over time, comparing them with another group that has not been affected by the condition or treatment being studied. Cohort studies

are observational and not as reliable as randomized controlled studies, since the two groups may differ in ways other than the variable under study.

Conflict of interest, according to WHO, is "any interest declared by an expert that may affect or reasonably perceived to affect the expert's objectivity and independence in providing advice" on the development of a guideline.

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

Cost–benefit analysis is a form of economic analysis in which both the costs and the consequences, including increases in the length and quality of life, are expressed in monetary terms.

Cost–effectiveness is the property of being effective or productive in relation to its cost.

Cost–effectiveness analysis is an economic analysis in which the consequences are expressed in natural units. Examples include cost per life saved or cost per unit of blood pressure lowered.

Cost implications are the cost consequence that may result from implementing a specific guideline or guidance on health care.

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

Cost–utility analysis is a type of cost–effectiveness analysis in which the consequences are expressed in terms of life-years adjusted by people's preferences. Typically, these consider the incremental cost per incremental gain in **quality-adjusted life-years**.

Declaration of interest, according to WHO, is the disclosure of any potential or actual conflicts of interest that include financial, professional or other interests relevant to the subject of the work or meeting in which an expert may be involved, and any interest that could significantly affect the outcome of the meeting or work. The declaration of interest must also include any relevant interests of others who may, or may be perceived to, unduly influence the expert's 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 *(5)*.

Dichotomous outcomes are any outcome measures in which there are two possibilities – such as dead/alive, admitted/discharged, pregnant/not pregnant – and where the patient must be in one, but cannot be in both categories *(6)*.

Economic evaluation is a set of formal, quantitative methods used to compare two or more treatments, programmes or strategies with respect to their resource use and expected outcomes.

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

Evidence summary/summary tables is a standard format – usually tabular – used to present a concise overview of clinical evidence.

Formal consensus is a systematic approach to eliciting agreement from a panel *(7).*

Grading of Recommendations Assessment, Development and Evaluation (GRADE) system is a collaborative working group that has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations used by many international organizations *(8)*.

Guideline advisory board (GAB) is the body whose tasks include the annual selection of potential guidelines for development out of proposed topics, and acceptance of the final guideline for approval.

Guideline panel develops and agrees on the recommendations in the guideline and endorses the final guideline document for approval by the **guideline advisory board (GAB)**. Another important task of the guideline panel is to facilitate implementation of the guideline at the national level.

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

Interventions are evidence-based options for diagnosis and care of patients, including prevention, pharmaceutical treatment, surgical techniques, patient education strategies and other types of therapeutic choice.

Medical subject headings (MeSH) is the United States National Library of Medicine's vocabulary thesaurus used for indexing articles for PubMed. It consists of sets of terms naming descriptors in a hierarchical structure that permits searching at various levels of specificity. http://www.nlm.nih.gov/pubs/factsheets/mesh.html.

National Institute for Health and Clinical Excellence (NICE) is a national health systems organization based in London and Manchester, United Kingdom. The organization works to ensure equal access to medical treatments and high-quality care from the National Health Service for citizens in England and Wales. NICE provides guidance, sets quality standards, and manages a national database to improve people's health and prevent and treat ill health *(9)*.

Outcomes are changes in health status that may occur in following subjects or that may stem from exposure to a causal factor or to a therapeutic intervention *(10)*.

Peer review is a process of subjecting scholarly works, research or ideas to the scrutiny of others who are experts in the same field *(11)*.

Population/patient-intervention-comparison-outcome (PICO) is a mnemonic used to remind health care providers of the four questions that are most helpful in developing a clinical question and assessing and determining a patient's care.

Quality-adjusted life-years (QALYs) are the number of years of expected life corrected for the quality of life that patients are expected to experience in those years *(12)*.

Quality assessment: see **Risk of bias assessment**.

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

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

Risk of bias assessment is a systematic assessment of characteristics of the design and conduct of clinical trials that have been shown to result in bias in the results – that is, estimates of the effect that are not accurate. It is also called "quality assessment" of clinical trials. See the Cochrane Handbook for full details *(13)*.

Scope provides the framework within which to conduct the guideline development work. Aspects the scope should define include:

- the population to be included or excluded;
- health care settings;
- types of intervention and treatment to be included or excluded;
- information and support for patients and care-givers;
- outcomes to be considered; and
- links with other relevant guidance.

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

Strength of recommendation/recommendation strength is the extent to which one can be confident that the desirable effects of an intervention or option outweigh their undesirable consequences. The strength of a recommendation has specific implications for patients, the public, clinicians, policy-makers and researchers (Table A1). This includes the following options.

- **Strong recommendation** – if the panel is highly confident of the balance between desirable and undesirable consequences, a strong recommendation for (desirable outweighs undesirable consequences) or against (undesirable outweighs desirable consequences) an intervention is offered.
- **Conditional recommendation** – if the guideline development group or panel is not very confident of the balance between desirable and undesirable consequences for the intended use of the recommendation, a conditional (also called weak) recommendation is offered. This may occur when the certainty of evidence is very low or low, or if values and preferences, cost, equity, acceptability, feasibility and other factors may depend on the setting where the intervention or option is implemented or are variable or uncertain.

Table A1. Interpretation of strong and conditional recommendations

Stakeholders	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	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.
Clinicians	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	It is important to recognize that different choices will be appropriate for individual patients and that each patient should be helped to arrive at a decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

Stakeholders	Strong recommendation	Conditional recommendation
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.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate (e.g. through use of decision aids or explicit consideration and documentation of the desirable or undesirable consequences related to an option or intervention).
Researchers	The recommendation is supported by credible research or other convincing judgements that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The 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 identify possible research gaps.

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

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

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The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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World Health Organization
Regional Office for Europe

WHO Country Office, Ukraine
58 Yaroslavska Street, 04071, Kyiv, Ukraine
Tel.: + 380 444285555 Fax: +380 444258828
Email: eurowhoukr@who.int
Website: www.euro.who.int