Roadmap

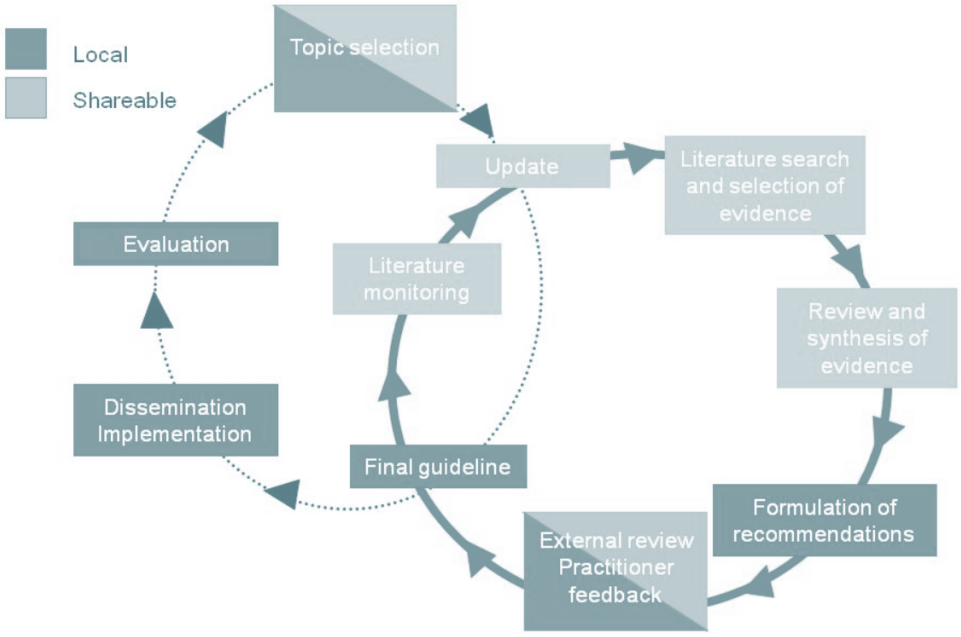
International Collaboration Project on the Development of Clinical Guidelines in Gynaecology & Obstetrics

INTRODUCTION

This roadmap provides a step-by-step guide for the development of evidence-based clinical guideline modules.

Three phases can be distinguished in the development process: 1. Preparation 2. Guideline development and 3. Completion and Implementation.

For each phase, we explain what actions have to be undertaken in collaboration and what actions are part of local policy. This document is intended for future international collaboration.



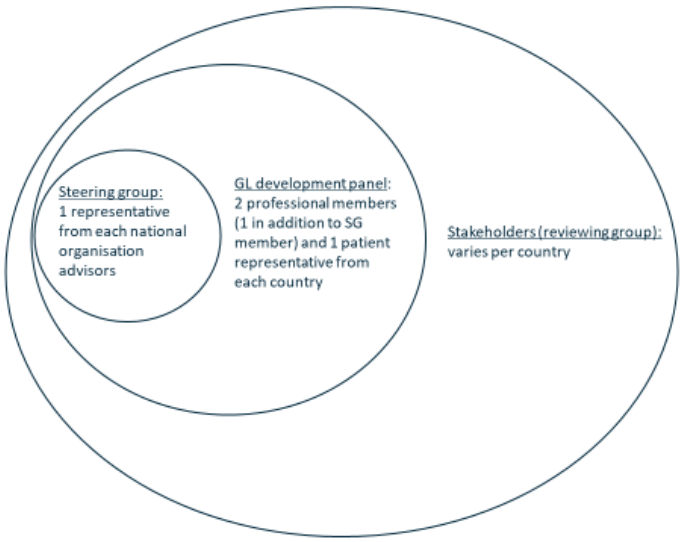
1. PREPARATION PHASE

The steering group prioritises topics for guideline development, adaptation or maintenance during the preparation phase. The reasons why a topic is chosen form the basis for further elaboration of a plan including composition of the guideline development group, mapping out the interests and choosing (a) form(s) of patient participation.

Regarding the choice of the topic for the guideline development, the following considerations may play a role:

- Potential health gains
- Severity of the condition
- Prevalence/incidence
- Societal impact
- Multidisciplinary approach
- Availability of evidence
- International differences/Health policy issues
- Level of controversy on the topic

Taking these considerations into account, the steering group chooses the topic of the guideline and proposes the draft of the clinical questions issued in the guideline.



A. COMPOSITION OF THE GUIDELINE PANEL

A guideline panel with a balanced composition of expertise forms the starting point for a guideline with broad support. It is important that there is room for open discussion, that no stones are left unturned and that all relevant aspects can be explored. The protocol ensures a balanced and responsible distribution of tasks over the relevant scientific disciplines and areas of interest. Often, the final guideline panel can only be determined after developing a list of issues concerning clinical practice (so-called problem areas) that will be addressed in the guideline.

Depending on the topic, the ratio between the delegation of panel members working in academic or teaching hospitals vs general hospitals and spread over a large geographical area, deserves attention. All panel members should have a mandate from their professional societies. In addition to health care providers, patients will also participate in the guideline development group, one patient representative per country, unless the members of the steering group from a particular country do not consider this feasible. If considered necessary by the steering group, a brief training in guideline development will be organised for professionals and for patient representatives. For the NVOG and RCOG involvement of patient or lay representatives is mandatory, and trained patient representatives are available.

Which steps?

One of the organisations chooses a chairman and is responsible for the chairman's functioning. A chairman should have no (financial) interests with regard to the topic of the guideline.
The primarily concerned organisations form the international guideline panel (in the pilot phase, these organisations were the NVOG, RCOG, DGGG and the VVOG) supplemented by delegates of the national patient organisation on the topic. Other organisations form the stakeholder reviewing group on a national level. In the pilot phase, these were the KNOV (Royal Dutch Midwives' Association), and the VBOV (Flemish Professional Organisation of Midwives).
Two members with clinical expertise in the topic of the guideline are to be mandated by each organisation. By mandating a guideline panel member, the organisations take into account any potential conflicts of interest with regard to the guideline topics.
Additionally, agreements will be made concerning periodic feedback and updating of the guideline.

B. MAPPING OUT THE POTENTIAL CONFLICTS OF INTEREST

When developing a clinical guideline, the improper influence on the recommendations due to conflicts of interest have to be prevented as much as possible.
It is important that the interests of the guideline panel members are identified. Furthermore, there should be a clear procedure for involvement and decision-making during development of the guideline in the case of reported interests. A transparent process contributes to the credibility and successful implementation of the guideline.
The English translation of the Dutch Code for the prevention of improper influence due to conflicts of interest will be used (https://storage.knaw.nl/2022-08/Code-for-the-prevention-of-improper-influence-due-to-conflicts-of-interest.pdf).

Which steps?

In order to make any conflicts of interests visible, the potential guideline panel members should fill out a declaration of interests before the first guideline panel meeting. Interests regarding personal financial interests, personal relations, reputation management, externally funded research and knowledge valorisation will be listed.
The completed declarations of interest are discussed with the whole international guideline panel at the beginning of the guideline process. The relevance of the declarations of interest will be confirmed upon publication. Patient representatives and methodologists will also fill out a declaration of interests. A concise summary of the declarations of interest of the guideline panel members will be attached (in tabular form) as an annex to the guideline.

How?

There are several ways to deal with conflicting interests:

- The guideline panel member will remain part of the guideline panel. He/she is provided with the opportunity to express his/her opinion during the research question and considerations' phase, but is not involved in formulating the recommendations on a specific topic.
- The guideline panel member will be excluded from the guideline panel, but is interviewed in order to contribute his/her expertise.
- The guideline panel member is excluded from the guideline panel altogether.

2. GUIDELINE DEVELOPMENT

A. LISTING OF PROBLEM AREAS AND IMPORTANT OUTCOMES

The development process will start upon completion of the preparatory steps; phase one. The first step in the guideline development phase (phase 2) is to develop a list of problems concerning the topic of the guideline. These can be submitted by all parties who are involved with the guideline topic (stakeholders). Each national organisation will perform this procedure in their own country in the way that is most convenient to them. During a written round in the countries that decide to perform this procedure, problem areas will be listed by stakeholders. The problem areas identified in the different countries will all be prioritised in one list by the guideline panel and translated into (final) key clinical questions. The list of problem areas will serve as a framework for the guideline.

Below we describe the procedure to be performed in the Netherlands. Organisations from other countries can run a similar or different procedure, or omit this step as preferred.

Which steps?

In addition to health care providers and care users (e.g. patient associations), other relevant parties may be approached to provide problem areas, for example, representatives of health insurances companies, (university) hospitals, and governmental organisations.
The list of problem areas is not limited to substantive medical problems and can include organisation, information and implementation problems as well as important outcome measures.
The stakeholders who have been approached, and the written contribution they subsequently make, must be documented and included in the guideline (present/not present, written input, reaction to the report, no reaction). The list of problem areas will be (if applicable) supplemented by the input from the patient focus group or other tools to let patients participate in the process.
A scoping review will be carried out to identify (international) guidelines, systematic reviews and literature on patient preferences.

How?

Steering group members state which stakeholders are relevant for the specific topic of the guideline and which stakeholders will be invited to the written round in their country. Professional associations are advised to gauge within their association whether these problem areas match the experiences of their participants.

In the Netherlands the invitation to the listing of problem areas will be sent to the following as standard:

- Netherlands Health Care Inspectorate
- Netherlands Pharmacovigilance Centre and the Trade association of pharmaceutical companies (if there is a concern about medications and/or heir potential adverse effects)
- Participating or allied medical specialists' organisations
- Patients' association(s)/ Dutch Patients' Federation
- Netherlands Care Institute
- Netherlands Health Insurers
- Dutch General Practitioners
- Royal Dutch Organisation of Midwives

This list can be supplemented with other relevant organisations, such as those representing paramedics. The organisations are asked to respond to the written list within four weeks.

The final list of problem areas from all countries in which this procedure is performed will be discussed by the guideline panel. The panel members will assign priority to each problem area. Based on this, a decision will be made about which problem areas will be addressed by the guideline. An overview of the problem areas that have been prioritized by the guideline panel for the guideline is fed back to the participants of the written round.

B. DEFINING KEY CLINICAL QUESTIONS AND RESEARCH QUESTIONS AND OUTCOMES

The prioritised problem areas in the framework are then converted into key clinical questions. The clinical questions will be (if required) reformulated in one or more specific research questions. These research questions can be answered using systematic literature research. The research question will be drawn up using the PICO methodology: Patient – Intervention – Comparison – Outcome. The result of the systematic literature research is a scientific conclusion. The scientific conclusion is internationally valid. A recommendation for practice can be made based on the scientific conclusion together with the considerations of the guideline panel. These recommendations may vary by country due to for instance differences in the healthcare systems in the different countries or differences in patients' values.

Carefully formulated clinical questions and research questions are an important prerequisite for the quality of the guideline and its timely completion. The risk of developing an insufficiently thought-through research question is that it will not be possible to find an answer, or that an answer will be provided that does not solve the underlying problem. Both scenarios can lead to the question needing to be reformulated and readdressed.

Which steps?

- Each clinical question will be assigned to a responsible panel member and a co-reader from a different country.
- The clinical question will be translated into a research question following the PICO method.
- An introduction will be written showing the reason for, and the importance of, the clinical question.
- The research question serves as the basis for a systematic literature search.
- If multiple interventions can be compared, it is important to identify those comparisons that will be important in clinical practice.

C. SELECTING, PRIORITISING AND DEFINING OUTCOMES

Only a number of the most important or critical outcomes will be chosen for the guideline. Examples of these outcomes are mortality, morbidity, pain, function, quality of life and complications. These outcomes must be prospectively selected and defined in order to focus on what is important for clinical decision-making and to prevent from focusing on selectively reported outcomes that may overestimate the treatment effect.

It is important that patients, and if applicable other (para)medical disciplines are also involved in selecting the important outcomes. Research will be evaluated for each outcome measure to determine whether the treatment makes a minimally clinically important difference. A minimally important difference means that the difference 'matters' to the patient.

Which steps?

- Outcomes will be prospectively selected and prioritised based on their role in clinical decision making.
- Important outcomes and any associated measurement instruments are defined.
- Both clinical and patient-oriented outcomes will be considered.
- A minimal clinically relevant difference will be defined.

How?

The guideline panel contributes by defining and considering important outcomes and the minimum clinically important difference for each outcome measure. The patients' perspective will thereby be taken into account.

D. FINDING AND SELECTING LITERATURE

The research question is answered by performing a systematic review. The literature search should be performed by a qualified clinical librarian, e.g. of the Knowledge Institute of the Netherlands Association of Medical Specialists; in the future the systematic reviews for separate key questions may be allocated to different participating countries. To find the literature, an information specialist of the country to whom the question has been assigned will develop a search strategy. A search strategy must be sensitive so that all relevant literature will be identified. The most well-known biomedical databases are Medline, Embase and the Cochrane Library. For therapeutic questions, a search will be carried out in multiple biomedical databases while, for diagnostic and prognostic questions, only one database will be searched.

When the literature search has been executed, a list of potentially relevant references has to be screened. The selection criteria are used to select potentially relevant studies. When an abundant number of references are found, the criteria will preferably be succinctly formulated in order to include a set of studies that is as homogeneous as possible. Homogeneity of studies contributes to the probative value of the results. The selection of articles must be objective, explicit and reproducible. Articles that do not comply with the selection criteria can be discussed in the considerations. A list of excluded articles with reasons of exclusion will be published with the guideline.

Occasionally, it will not be possible to include any studies, which means the research question cannot be answered with evidence from the literature. In this case, the clinical question should be answered on the basis of clinical expertise.

Which steps?

- The search form will be filled out by a guideline panel member.
- Selection criteria will be established by a guideline panel member.
- The research strategy will be established and executed by a qualified information specialist from the country to whom the question has been assigned.
- The study selection on title and abstract will preferably be carried out by two guideline panel members who make a selection independently.
- Full text of articles selected on title and abstract will be reviewed in more depth.
- An overview of included and excluded articles will be generated and published with the guideline.

How?

Guideline panel members deliver a number of key articles that answer the research question and that meet the stated inclusion criteria. Search terms can be extracted from the key articles and used to find out how the article is indexed in the databases. Finally, the key article can be used to check the search strategy by verifying whether the named article is also found using the search strategy.

The study selection should preferably be carried out by someone with extensive knowledge of the topic and backgrounds. This is why this is the responsibility of the members of the guideline panel.

E. REVIEWING AND SUMMARISING LITERATURE

Limitations in the study design can seriously affect the results of a study. Therefore, it is important to present the scientific basis for each research question as objectively and transparently as possible. The conclusion of the research question will be graded and reported according to Grading of Recommendations Assessment, Development and Evaluation methods (GRADE). GRADE is the international standard for guideline methodology.

Which steps?

- The study characteristics and results of critical and important outcomes will be described in evidence tables.
- The risk of bias will be assessed with validated instruments for each study and displayed in risk of bias tables.
- If possible (depending on the clinical and statistical heterogeneity), a meta-analysis will be carried out.
- For each outcome, the quality will be graded according to GRADE and reasons for upgrading or downgrading will be described (see Table 1 & Table 2). The quality reflects our confidence that the effect estimates are adequate to support a particular recommendation.
- An overall conclusion according to GRADE will be established for all outcomes together. The lowest quality is leading.

How?

Studies to be included are summarised and reviewed by an advisor. The data are summarised in evidence tables, and the Risk of Bias assessment of the individual studies is examined. Depending on the results, a meta- analysis may or may not be carried out. A meta-analysis means that results from selected studies are pooled and analysed as if they were a large study population (see Figure 2 for an illustration), taking into account the relative size of the individual studies. However, when the results of the studies are very heterogeneous, one should refrain from a meta-analysis and study results must be discussed qualitatively.

A conclusion will be drawn for each outcome measure with appropriate quality of evidence according to the GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation). The quality of evidence is assessed on four levels: high, moderate, low or very low. Within GRADE methodology, RCTs start with high quality and observational studies with low quality. Five factors are assessed that can lower the quality of the evidence and three factors that can increase the probative value for each outcome (see Table 1 & Table 2). The quality can be reduced by one or two levels for each factor. If there is a serious restriction, the quality will be downgraded by one level; if it is a very serious restriction, the quality will be downgraded by two levels. The same principle applies for upgrading the quality of evidence.

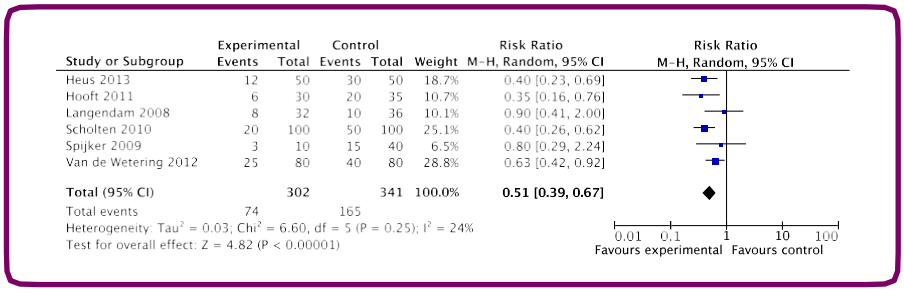


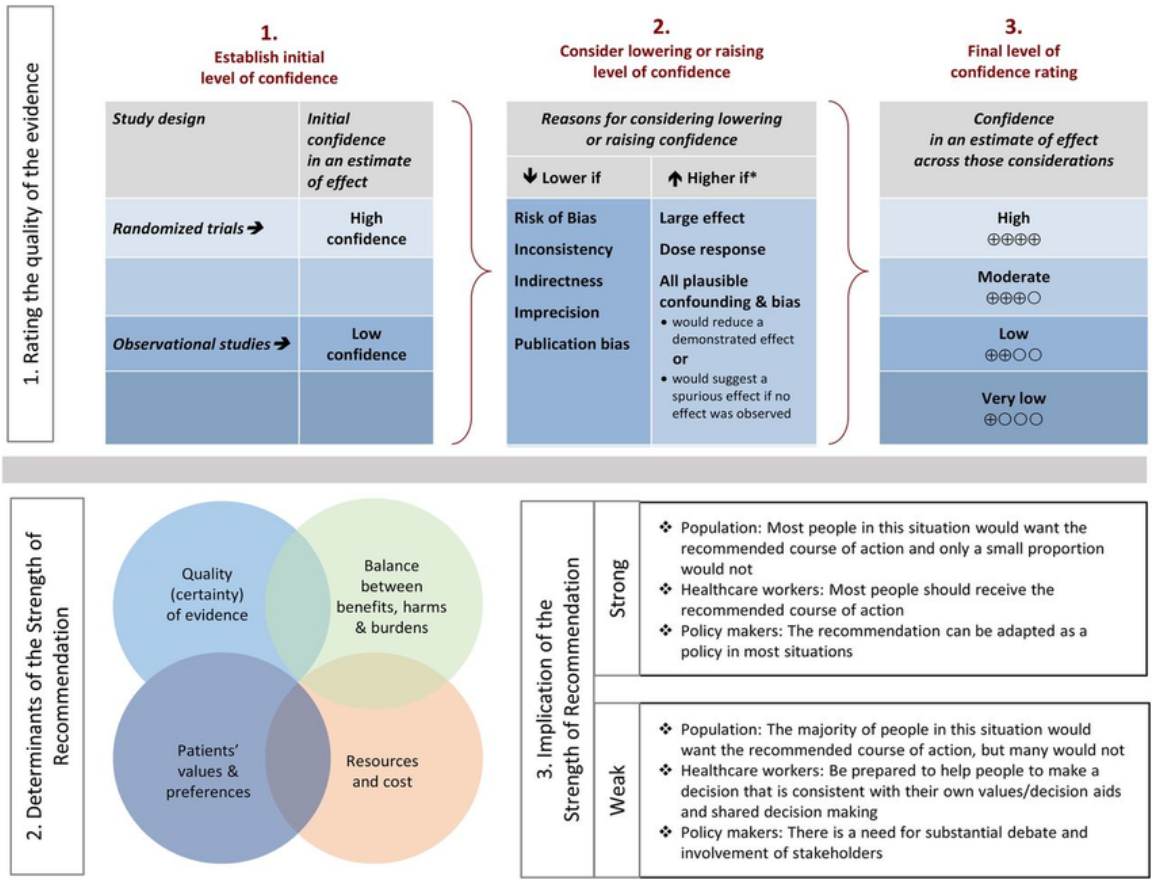
Figure 2. A hypothetical meta-analysis in which the individual results of six studies are combined into an overall effect estimate (average weighted effect estimate): a relative risk (Risk Ratio) of 0.51 with a 95% confidence interval of 0.39 to 0.67.

Table 1. Factors that can reduce the quality of the evidence

Factor	Consequence
Study limitations	↓ 1 or 2 levels
Inconsistent results	↓ 1 or 2 levels
Indirectness of evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Distortion by incomplete reporting (publication bias or selective reporting of results)	↓ 1 or 2 levels

Table 2. Factors that can increase the quality of evidence

Factor	Consequence
A very large magnitude of effect	↑ 1 or 2 levels
All plausible confounders may be working to underestimate the true treatment effect	↑ 1 level
Evidence for a dose-response gradient	↑ 1 level


1. Rating the quality of the evidence
1.
Establish initial level of confidence
Study design
Initial confidence in an estimate of effect
Randomized trials
High confidence
Observational studies
Low confidence
2.
Consider lowering or raising level of confidence
Reasons for considering lowering or raising confidence
Lower if
Higher if*
Risk of Bias
Inconsistency
Indirectness
Imprecision
Publication bias
Large effect
Dose response
All plausible confounding & bias
would reduce a demonstrated effect
or
would suggest a spurious effect if no effect was observed
3.
Final level of confidence rating
Confidence in an estimate of effect across those considerations
High
Moderate
Low
Very low
2. Determinants of the Strength of Recommendation
Quality (certainty) of evidence
Balance between benefits, harms & burdens
Patients' values & preferences
Resources and cost
3. Implication of the Strength of Recommendation
Strong
Population: Most people in this situation would want the recommended course of action and only a small proportion would not
Healthcare workers: Most people should receive the recommended course of action
Policy makers: The recommendation can be adapted as a policy in most situations
Weak
Population: The majority of people in this situation would want the recommended course of action, but many would not
Healthcare workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making
Policy makers: There is a need for substantial debate and involvement of stakeholders

F. FROM EVIDENCE TO RECOMMENDATIONS

The conclusions from the systematic literature analysis form the answer to the research question but is often not necessarily applicable as a recommendation in daily practice. To answer the clinical question, other aspects must therefore be taken into consideration as well. Therefore, before a recommendation is formulated, values, preferences and resource use must be weighted as well. These considerations will be described explicitly and systematically, presenting arguments both in favour and against the examined care options. The method for the assessment and consideration of the results of the systematic literature analysis will be presented in a final paragraph. Considerations will always be described, if necessary entirely or partially on a national level. In the event that no studies have been found to answer the research question, the recommendation will be based on the considerations alone. For the (substantiation of the) considerations, it is possible to use (international) guidelines, consensus statements and expert opinion articles.

Which steps?

The considerations will be described on international and national level:

- The first part of the considerations reflecting the more methodological part can be described by the guideline development group as a whole.
- Balance between desirable and undesirable effects (health benefits, side effects, therapy compliance and risks).

The next parts of the considerations may be locally/nationally influenced and can be entirely or partially formulated by the national subgroups:

- Implications for implementation including costs, required resources and time.
- To what extent the results of the studies can be extrapolated to national practice.
- Values and preferences of patients as they were presented in a focus group and/or literature obtained from the research on the patients' perspective. Expertise of the care providers.

How?

The considerations relevant to formulate the recommendations will be described by the guideline development panel as a whole when it concerns methodological issues. This will result in attention being paid to the manner in which the guideline panel has reviewed and weighed these considerations with the scientific conclusions. Then other considerations can be formulated. It is an option to use the international Evidence to Decision framework to formulate the recommendations. The following topics need to be addressed:

- Pros and cons of the intervention and quality of the evidence
- Values and preferences of patients (and their caregivers)
- Costs
- Acceptability, feasibility and implementation
- Differences between countries

G. FORMULATION OF RECOMMENDATIONS

A recommendation is an answer to the clinical question. The recommendation provides, on the basis of a careful weighing of the obtained conclusion from the

systematic literature research and any additional considerations, a concrete and unambiguous description of the best care option. The strength of the recommendation is determined by weighing up all the relevant arguments together. In accordance with GRADE methodology, a low quality of evidence from the systematic literature analysis does not rule out a strong recommendation, while weak recommendations are also possible with a high quality of evidence.

Which steps?

- Recommendations are based on both the scientific conclusion and the considerations (they should be traced from the text and should not 'appear out of the blue').
- Recommendations will be formulated in an active, clear and unambiguous way.
- Formulations with 'consider' will be avoided as much as possible.
- Recommendations will preferably be formulated including the criteria that can provide direction for the choice between treatment options: a strong or conditional recommendation.
- The quality of evidence and the considerations affect the strength of the recommendation.
- A recommendation will be emphatically formulated where possible but offers space when necessary.

How?

It is important to formulate clear recommendations that meet the needs of clinical practice. Recommendations have implications for clinical practice.
As clinical practice can differ between different countries, the recommendations may be formulated separately or by the guideline development panel as a whole.

3. COMPLETION AND IMPLEMENTATION

A. DEVELOPMENT OF ANY RELATED PRODUCTS

A guideline is an instrument that cannot be seen in isolation from other, quality-improvement oriented products. These products are, for example, aimed at dissemination and implementation. Products will also be developed that stimulate scientific research into the most important knowledge gaps concerning the topic of the guideline.

In the Netherlands there should always at least be a product for patients (patient information), an implementation plan and a list of knowledge gaps (topics for further research). The choice for addressing other related products depends on the topic (relevance), the expected barriers for implementation, and the needs of the medical specialists' organisation(s), patient association(s) and umbrella organisation(s).

Notes on the related products:

- Product for patients: a product (e.g.: folder, patient version of the guideline, decision aid) will be developed for each country by panel members together with their national organisations.
- Implementation plan: the timelines for implementation, the expected impact on costs, and conditions will be mapped out for each recommendation per country. This results in a number of factors that may impede the implementation of the guideline. For each factor, a possible solution and responsibilities will be described.
- List of knowledge gaps: during the development of the guideline, some questions will remain unanswered because no (high-quality) studies have been carried out. This is an international issue. These gaps in knowledge will be gathered together during the development process. The guideline panel prioritises the most important knowledge gaps and formulates research questions for these gaps.

B. AGREEMENTS ON KEEPING THE GUIDELINE UP TO DATE

To be able to give patients the best care, it is important that guidelines follow the latest developments and scientific insights within a specific field. In order to keep existing guidelines up to date, it is important to make agreements about the validity period and revision of the guideline modules upon completion of the development process.

C. COMMENTARY PHASE

The aim of a commentary phase is to allow the contents of the guideline to be checked by stakeholders so that it can be adjusted where necessary. During the commentary phase, all parties that were invited for the problem area analysis and patients who participated in the patients' focus group are provided with the opportunity to respond to the draft texts.

Which steps?

Once the draft guideline texts are ready, the draft guideline will be offered to all participating organisations, the organisations involved in the listing of problem areas

at the beginning of the procedure, and any patients who may have participated in a patients' focus group for comment.
The organisations will check the content and applicability of the guideline. The response term is usually eight weeks.

How?

After receiving the draft guideline, organisations distribute the guideline amongst their members. The organisations collect the comments in the comments table, which will be attached. The panel members respond to those comments they think are crucial and adapt the text of the recommendations if necessary.
At the end of the commentary phase, each organisation will receive an overview of the comments and responses.

D. AUTHORISATION

Authorisation is the formal ratification of the guideline by the parties involved in developing the guideline. When a professional group ratifies a guideline, the guideline is included in the professional standard of care. Deviations from the guideline are allowed, but must be justified in the patient's file.

Which steps?

When the commentary phase has been finalised, the comments will be processed. Following which, the guideline is sent for authorisation to the relevant organisations in each country.

- Participating patients' organisations will be asked to endorse their suggested problem area (if applicable).
- The authorisation phase is normally completed within three months.

E. PUBLICATION

A condition for implementation of the guideline is that it is easy to find.

Which steps?

After authorization, the guideline will be published at 'richtlijnendatabase.nl', the G-I-N and local and national professional websites.

Phase	Activities	By whom?	Internationally or nationally?
1. Preparation			
	Choice of topics	Steering group	I
	Formulation of draft clinical questions	Steering group	I
	Composition of guideline development group	Steering group, national organisations	I
2. Guideline development			
	Listing of problem areas and important outcomes	Stakeholders (reviewing group)	N
	Prioritisation of problem areas	GL panel	I
	Formulation of clinical questions	GL panel	I
	Defining key clinical questions, research questions and outcomes	GL panel	I
	Selecting and prioritizing outcomes and determining MCIDs	GL panel	I
	Finding literature	Clinical librarian	I
	Selecting relevant literature	GL panel	I
	Reviewing and summarizing literature	Pilot: Knowledge Institute NL	I
	Description of considerations	GL panel	both I and N
	Formulation of recommendations	GL panel	N (sometimes I)
3. Completion and implementation			
	Development of any related products	GL panel	N
	Keeping the GL up to date	GL panel	I
	Commentary phase	Stakeholders	N
	Authorisation	Relevant organisations	N
	Publication	GL panel	both I and N