manual

for

ESHRE guideline development

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Summary

Aim
The principal aim of this manual is to provide a stepwise practice tool for members of ESHRE guideline development groups (GDG). It is expected that its systematic approach will improve the methodological quality of ESHRE guidelines and thus have a positive impact on the quality of reproductive healthcare in Europe.

The manual is based on recent literature on international guideline development methodology and on the internationally acceptable criteria of methodological quality, as articulated by the Appraisal of Guidelines for Research and Evaluation in Europe (AGREE) instrument (www.agreetrust.org).

Clinical practice guidelines
Clinical practice guidelines are defined as “systematically developed statements to assist care providers and patient decisions about appropriate health care for specific clinical circumstances” and should be helpful in everyday clinical practice.

ESHRE guidelines
ESHRE clinical guidelines contain recommendations on a particular clinical issue (e.g. male subfertility, endometriosis, PCO syndrome) and are based on the best available evidence (most relevant and highest level of evidence) and not on all evidence available.

In general it is recommended that ESHRE guidelines are kept to a reasonable size in order to ensure their development within an 18-24 month period. A fixed budget will be available to cover the costs of two meetings incurred in the running of a GDG.

ESHRE guideline development stepwise
Guideline development, implementation and evaluation is no linear process, but a cycle of interdependent activities (figure 1.1). The steps within this process are:

1. guideline topic selection
2. formation of the guideline development group
3. scoping of the guideline
4. formulation of the key questions
5. search of evidence
6. synthesis of evidence
7. formulation of recommendations
8. writing the guideline’s draft version
9. consultation and review
10. guideline dissemination
11. guideline implementation and evaluation and
12. guideline updating.

1. Guideline topic selection

The Executive Committee of ESHRE will once a year invite all ESHRE members, but in particular the Co-ordinators of the Special Interest Groups (SIGs) to propose new guideline topics by application form. This form mainly requests information about the relevance of the proposed clinical problem (e.g. volume, costs and patient impact), expected benefits from a guideline in, for instance, reduction in actual practice variation, and the availability of evidence or guidelines on this subject.

All proposals will be prioritized and considered for selection by the SIG Safety & Quality in ART (SQUART) Deputies. However, the final decision is made by the Executive Committee.

2. Formation of the guideline development group (GDG)

Once a topic for guideline development has been selected, the applicant is asked to propose a chairperson for the GDG. A chairperson is officially invited and nominated by the Deputies of the SIG SQUART. Subsequently, they will form a GDG.

The composition of an ESHRE GDG should reflect the range of stakeholders and include at least content expert(s), non-expert clinician(s), allied health care provider(s) and an ESHRE research specialist. Patients or their representatives can also have per guideline one ESHRE GDG member. In total a maximum of six to nine GDG members is recommended and geographical and gender balance should have been considered.

A GDG chair is appointed for a period of four years. He/she and all additional GDG members should declare any conflicts of interest and confidentiality. They will all be offered a two-day workshop on evidence based guideline development to increase and equal the level of guideline development expertise within a GDG.

3. Scoping of the guideline

Guideline development starts with defining the overall objectives of the guideline (e.g. potential impact and benefits), the patient and target users, and its relation to other (ESHRE) documents. After consensus on what is within and outside the scope of the guideline, its range can be defined according to a checklist and evaluated for (valid) completeness, European view and feasibility. Once the scoping is complete, the guideline's key questions are formulated.

4. Formulation of the key questions

Effective and efficient guideline development demands asking and answering key questions. Those key questions should be clear, focused and closely define the boundaries of the topic. A helpful framework to format systematically the different parts of a key question is the PICO framework, which has four components: Patients/population, Interventions, Comparisons and Outcomes.
About 15-20 key questions for one guideline would be a reasonable number.

5. Search of evidence

The first step in the search for evidence is to look for existing guidelines discussing the same question(s) by screening a list of websites.

Next, the key questions should be translated into key words and the search gathered into a systematic process to avoid or minimize bias. To select only the best available evidence (most relevant and highest level of evidence, and not all the evidence available), evidence should be identified in the following order: systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, observational studies and finally case reports/opinion documents.

An ESHRE research specialist will be available to conduct the literature searches, but GDG members will have to initiate the search by completing an ESHRE literature search request form with provision of the search terms and limitations.

Although the research specialist will perform a preliminary level of sorting based on title and abstract, the clinical expertise of GDG members will be necessary to carry out a definitive sifting of the search output.

6. Synthesis of evidence

Studies identified during the stepwise literature search must be reviewed to identify the most appropriate data. This involves four major steps: selecting relevant studies; assessing their quality; synthesising the results; and grading the evidence.

First, the titles and abstracts are scanned for relevance to the key questions and fulfilment of the selection criteria agreed by the GDG. Secondly, the quality of each study is assessed by means of a checklist to ensure its validity and applicability. To minimise any potential bias independent assessments are performed by two reviewers (ESHRE research specialist and the responsible GDG member). Assessment differences are discussed to reach consensus. Thirdly, after this final selection, the available evidence will be summarized according to a standard template (evidence table) which identifies key characteristics of the study population (e.g. sample size, age), intervention (e.g. follow-up period, kind of intervention), comparison (e.g. IUI versus timed intercourse) and outcome measures (e.g. effect size). These evidence tables are stored and published as supporting materials of a guideline.

Finally, the selected evidence must be graded. This grading is related to the strength of the supporting evidence. There are three levels of evidence (level A, B and C).

7. Formulation of recommendations

After the selection and summary of the evidence its content should be condensed into recommendations. ESHRE suggests a standardized phrasing in which the recommendations are classified (Class I, IIa, IIB and III).

An ESHRE guideline recommendation should be a stand-alone text written in a complete sentence, containing enough detailed information to be understandable without references to supporting material and should answer one of the key questions. A help to guarantee the formulation of such clear

recommendations is the five 'W' rule: each recommendation should be a description about **who** does **what** for **whom, when** and in **which way**.
When the GDG has reached consensus about the formulation of recommendations, the draft version of the guideline can be written.

8. Writing the guideline's draft version

ESHRE guidelines should be written in English and with a European scope. Furthermore, they should be comprehensive and flexible enough to allow adaptation to diverse settings and circumstances of clinical practice. For guideline uniformity an ESHRE guideline is written according to an established structure consisting of five main parts in the following order:

- guideline background (e.g. GDG members, review panel)
- general introduction (e.g. epidemiology, treatment options, probable outcomes)
- summary (e.g. list of all recommendations)
- key question-related part (e.g. explicit links between recommendations and available evidence) and a final
- general part (e.g. disclaimer).

9. Consultation and review

The final stages of guideline development involve review by its future users and approval by the parties involved, the SQUART's Deputies and finally the ESHRE Executive Committee. Within this phase the adequacy of the guideline document is evaluated, particularly for clinical content, methodological quality, and applicability.

Firstly, all members of the ESHRE Advisory Committee, the SIGs involved and some patients' representatives (lay reviewers) are invited to review the draft. Interested reviewers have to disclose any potential conflicts of interest and send in their review comments strictly time-limited within six weeks.

Secondly, the guideline's draft is posted on the ESHRE website and all ESHRE members are invited to review.

Finally, after integration of the reviewers' comments, the revised version combined with a comments processing report is sent for a methodology check to the SQUART's Deputies. This methodology check is primarily based on the principles outlined in this manual and the validated AGREE Instrument.
Final approval is given by the ESHRE Executive Committee.

10. Guideline dissemination

Dissemination involves making guidelines accessible, advertising their availability, and distributing them widely. A range of dissemination strategies can be effective, but there is too little evidence to support decisions about which strategy is efficient under which circumstances. In general, the use of multi-faceted dissemination strategies is recommended.

The standard dissemination procedure for all ESHRE guidelines should involve publishing (ESHRE website, Human Reproduction and National Guidelines Clearinghouse's website) and announcement (Focus on

Reproduction, newsflash ESHRE website, news item in the digital ESHRE newsletter, annual ESHRE meeting, related National Societies and all appropriate remaining stakeholders). It is recommended that a full-length version of a guideline combined by a short summary is published.

ESHRE guidelines can also be adapted and translated by National Societies.

11. Guideline implementation and evaluation

Guidelines do not implement themselves; local ownership of the implementation process is crucial for changing practice. ESHRE is responsible for the development of European guidelines and their implementability, but not directly for their implementation into local practice. However, the Guideline Implementability Appraisal instrument can be helpful for identifying obstacles to implementation. And in general, focussing on individual recommendations, rather than on the guideline as a whole, makes implementation initiatives more manageable.

At an appropriate time after guideline dissemination and implementation an evaluation is necessary for insight into its impact. Such an evaluation can consist of several components, such as practice performance measured by a clinical audit and indicators (measurable elements of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality of care provided).

12. Guideline updating

Guidelines should be kept up to date. All ESHRE guidelines will carry a statement indicating that they will be considered for revision four years after publication. In addition, every two years after publication searches for new evidence are performed and updating may be considered.

For a full revision the application procedure and renewed recruitment of GDG members should follow the usual process described in this manual.

Chapter 1

Introduction

Aim of this manual

The principal aim of this manual is to provide stepwise advice to individual members of ESHRE guideline development groups (GDG). The expectation is that this approach will improve the methodological quality of ESHRE guidelines and will have a positive impact on the quality of European reproductive healthcare.

The manual draws on the most up-to-date evidence on international guideline development methodology and resources available, such as manuals/handbooks for guideline development from the:

- American College of Cardiology Foundation and American Heart Association (ACC/AHA)[1] (www.americanheart.org)
- Dutch Institute for Healthcare Improvement (CBO)[2] (www.cbo.nl)
- Canadian Medical Association (CMA)[3] (www.cma.ca)
- European Society of Cardiology (ESC)[4] (www.escardio.org)
- National Health and Medical Research Council (NHMRC)[5] (www.nhmrc.gov.au)
- National Institute for Health and Clinical Excellence (NICE)[6] (www.nice.org.uk)
- New Zealand Guidelines Group (NZZG)[7] (www.nzzg.org.nz)
- Scottish Intercollegiate Guidelines Network (SIGN)[8] (www.sign.ac.uk)
- World Health Organization (WHO)[9] (www.who.int).

In addition, the manual is based on internationally acceptable criteria of methodological quality, as articulated by the Appraisal of Guidelines for Research and Evaluation in Europe (AGREE) instrument (www.agreetrust.org).

The structure of this manual follows guideline development from its proposal through to publication and beyond.

This ESHRE manual is intended to be a “living” publication. Comments on either content or presentation are welcome and should be sent to bruno@eshre.com At the time of change, GDG members will be notified.

Clinical practice guidelines

Clinical practice guidelines are defined as “systematically developed statements to assist care providers and patient decisions about appropriate health care for specific clinical circumstances”[10]. Clinical guidelines are intended as neither cookbook nor textbook, but should be helpful in everyday clinical medical decision-making about appropriate and effective care. Therefore, clinical guidelines should be presented in formats easy to interpret.

Throughout the past decade, the focus in clinical guideline development has been increasingly on systematic evidence selection and summarization in order to develop more evidence based recommendations[11]. However, this requires a rigorous approach involving various stakeholders and perspectives. Although there is consensus on the essential steps in guideline development, there has been less progress in ensuring that recommendations of clinical practice guidelines are fully implemented.

ESHRE guidelines

The main goal of ESHRE guideline development is the provision of clinical recommendations to improve the quality of health care delivery within the European field of human reproduction and embryology.

ESHRE guideline development methodology complies with the criteria used by the AGREE instrument for good quality guidelines. Most of these criteria are located as tips at the end of each chapter.

ESHRE clinical guidelines contain recommendations on a particular clinical issue (e.g. male subfertility, endometriosis, PCO syndrome). These guidelines are based on the best available evidence (most relevant and highest level of evidence) and not on all evidence available. There is an explicit link between recommendations and their available evidence. Furthermore, scientific and clinical evidence take precedence over expert judgement.

Although the issue of economic considerations and implications might be addressed in ESHRE guidelines, this is not their main aim and is sometimes impossible because of the obvious differences in current European economic and healthcare systems.

Moreover, ESHRE guidelines can be adapted and translated by National Societies ensuring more efficient use of resources and improvement of patient outcomes throughout Europe. ESHRE guidelines should therefore be flexible and adaptable such that individual circumstances can be taken into consideration.

Finally, ESHRE guidelines can be used in the education and training of healthcare professionals and can facilitate the communication between patients, healthcare professionals and European policy makers.

Medico-legal implications of ESHRE guidelines

Potential medico-legal implications of clinical guidelines have been of ongoing concern to medical practitioners[12]. However, clinical guidelines are intended as an aid to clinical judgement, not to replace it. The ultimate decision about a particular clinical procedure or treatment will always depend on each individual patient's condition, circumstances and wishes, and the clinical judgement of the healthcare team as is represented within the disclaimer at the end of each guideline. Clinical guidelines do not rob clinicians of their freedom, nor relieve them of their responsibility to make appropriate decisions based on their own knowledge and experience only.

ESHRE guideline development stepwise

Guideline development, implementation, and evaluation is no linear process, but a cycle of interdependent activities. Key steps within this process are: topic selection, synthesis of evidence, formulation of recommendations, consultation and review, dissemination and implementation, evaluation and updating (figure 1.1).

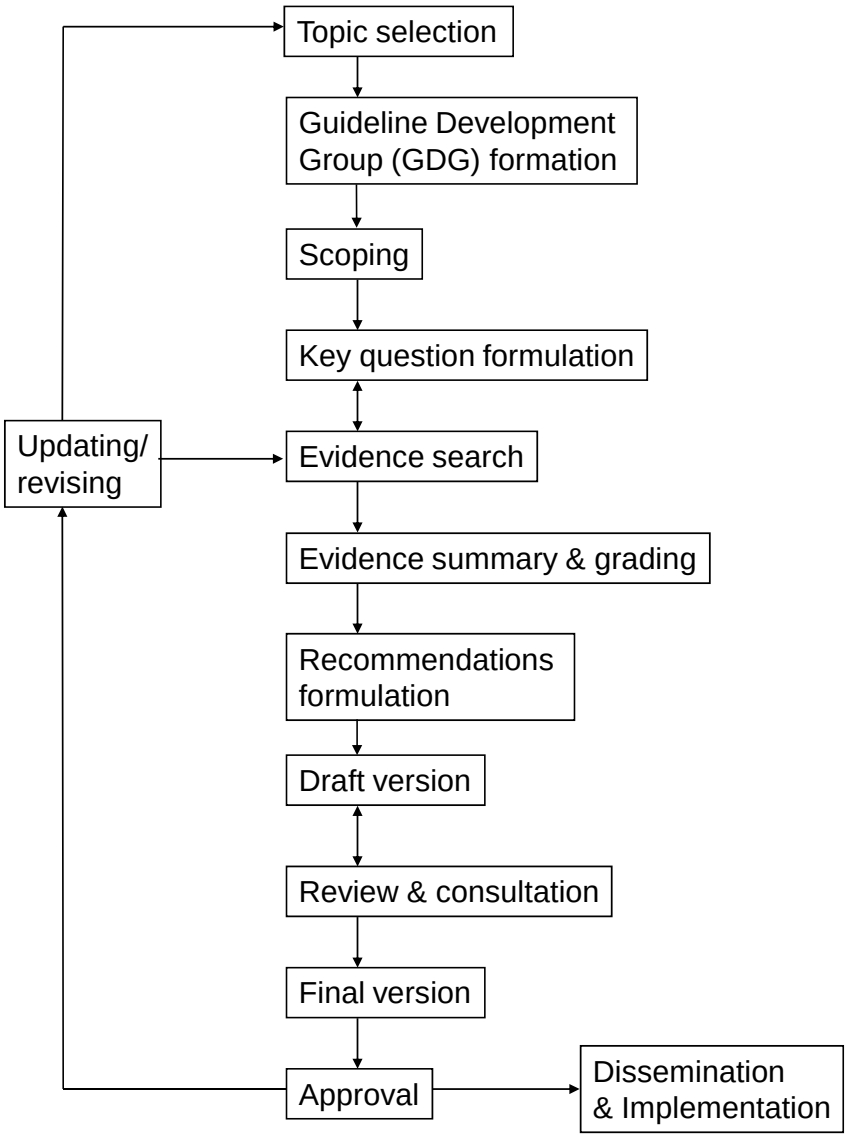

Figure 1.1 Schematic stepwise guideline development

Timelines
The time taken to develop an ESHRE guideline varies according to the scope of the topic, the volume of relevant literature, the amount of feedback received and the time needed to reach consensus about some topics. In general it is recommended to keep the guideline to a reasonable size to ensure its development within an 18-24 month period.

Budget
In an effort to cut costs and time, it is strongly recommended to organize free meetings in conjunction with other meetings/congresses. The use of Internet, e-mails and teleconference for communication is also strongly encouraged to increase efficiency and avoid unnecessary meetings and travel.

A fixed budget is set to cover the costs of two meetings of a Guideline Development Group (GDG). These expenses cover meeting costs, including travel (economy class tickets), accommodation, food and meeting facilities. Costs are reimbursed upon request within four weeks, on presentation of original receipts, invoices, bills, tickets etc., to be submitted to the ESHRE Central Office (address: Meerstraat 60, 1852 Grimbergen, Belgium/Fax: +32 (0)2 269 56 00/E-mail: info@eshre.com

According to this budget the proposed timescale for ESHRE guideline development is represented in figure 1.2.

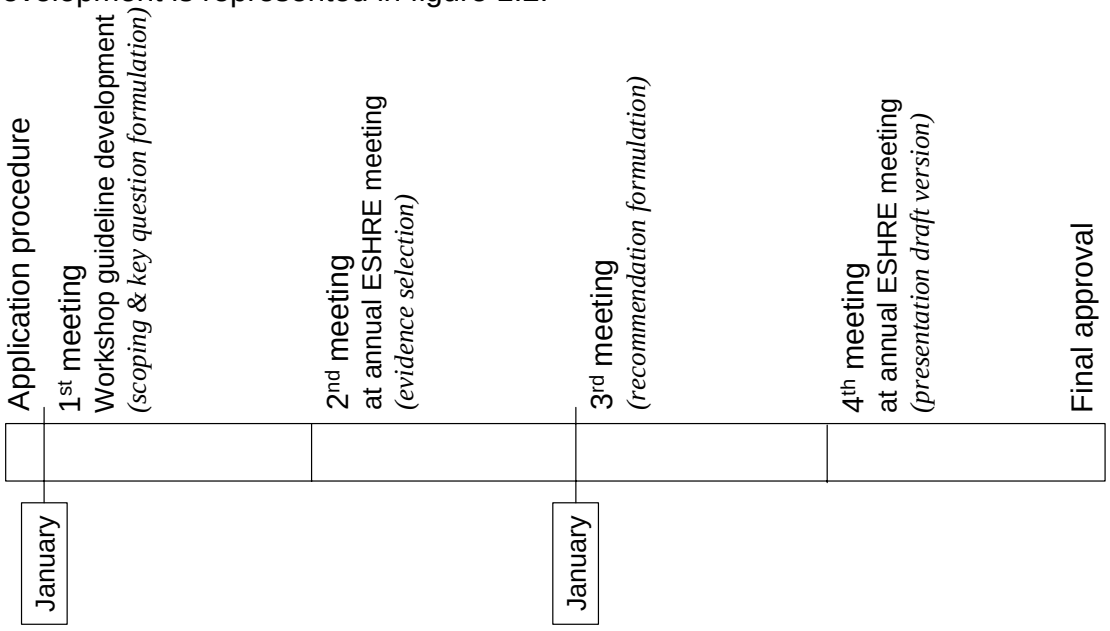

Figure 1.2 Schematic timescale for ESHRE guideline development

Chapter 2

Selecting guideline topics

Selection procedure

The Executive Committee of ESHRE invites the Co-ordinators of all Special Interest Groups (SIGs) to propose once a year new guideline topics. These proposals are made on an application form (Appendix A), and subjects chosen are within the field of reproductive medicine and embryology with the aim of assisting physicians and laboratory staff in diagnosis and/or clinical management.

Individual ESHRE members wanting to present a guideline topic can do so in collaboration with the ESHRE Advisory Committee using the same application form. Members should therefore contact their own country's representative.
After the expiry date, all proposals will be prioritized and considered for selection by consensus among the SIG Safety & Quality in ART (SQUART) Deputies. The final decision is made by the Executive Committee.

Application procedure

The standard guideline application form can be downloaded from the ESHRE website http://www.eshre.com/ESHRE/English/SIG/Safety-Quality-in-ART/Manual-for-ESHRE-Guideline-Development/page.aspx/254
This form requests information about:

- contact person(s) and involved SIGs
- relevance of the proposed clinical problem (e.g. volume, costs, patient impact)
- outcome(s) to be addressed by the proposed guideline
- variation in actual practice
- expected benefits from guideline development and implementation
- inventory of existing guidelines within the field
- indicated size and strength of the evidence base.

To check the presence of existing guidelines the following websites should be screened: Guidelines International Network (www.g-i-n.net), National Guideline Clearinghouse (www.guideline.gov), American Society for Reproductive Medicine (www.asrm.org) and the National Institute for Clinical Excellence (www.nice.org.uk). The Cochrane Library (at least) should be consulted for existing evidence.

Selection criteria

Appropriate topic selection is important to ensure that an ESHRE guideline is relevant and addresses priority issues for the improvement of European reproductive medicine.

Within the selection procedure priority is given on topics with:

- high volume
- high costs
- major patient impact (e.g. health burden or high risks)
- high practice variation
- high improvement potential.

Topics ranked highest are included in ESHRE's guideline development programme, depending on capacity. Topics which are not accepted but have a high ranking will be reconsidered at the next topic prioritization alongside new proposals. If the proposal receives a low ranking, it will be returned to the concerned SIG or the Advisory Committee for reconsideration or revision.

Updating existing guidelines

The same application form must be used for updating existing ESHRE guidelines (total revision), but the priority and selection procedure are independent of the procedure for new suggested guideline topics.

Steps

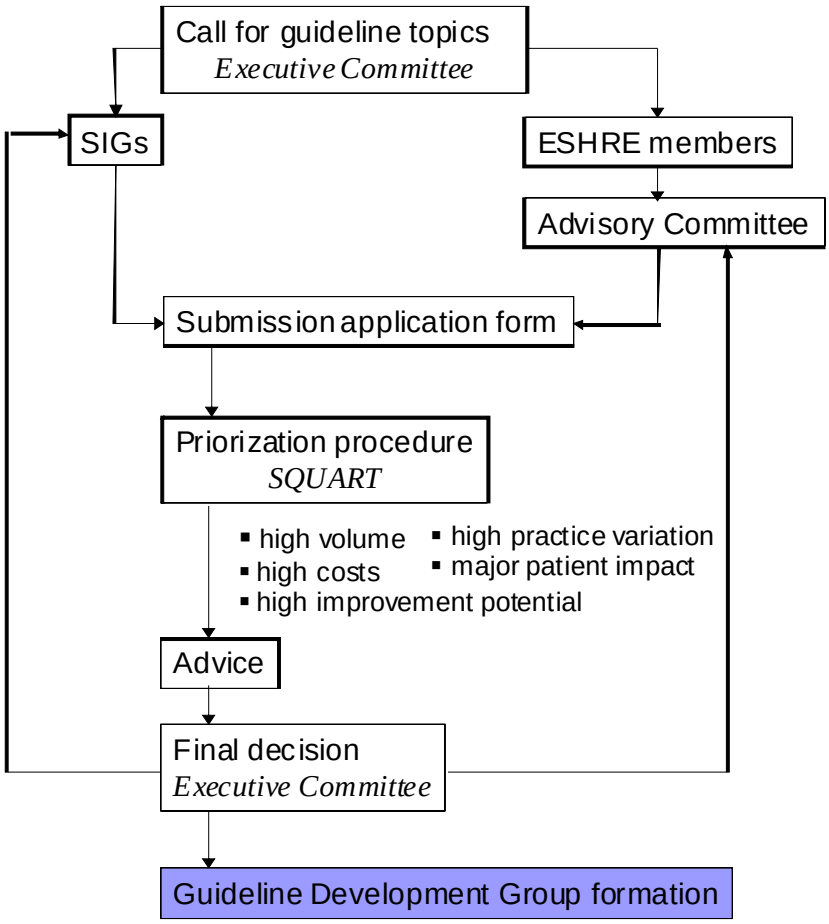

Figure 2.1 Schematic stepwise topic selection

Chapter 3

Forming guideline development group

Convening an effective guideline development group (GDG) is a crucial stage in producing a guideline; the GDG agrees the key questions, considers the evidence and has considerable influence on the final guideline recommendations[13]. Therefore, the Institute of Medicine strongly recommends the participation of representatives of all key groups and disciplines affected by a guideline topic[14].

Recruitment procedure
When the Executive Committee has selected a topic for guideline development it informs the applicant and invites him/her to propose a chairperson of the GDG to the SIG SQUART's Deputies. When agreement is reached, the proposed chairperson is officially invited and nominated by the Deputies of the SIG SQUART. Subsequently, the chairperson and SIG SQUART's Deputies put together a balanced and independent GDG. Potential members should not be contacted before their membership has been approved by the SIG SQUART. Finally, the SIG SQUART's Deputies formally invite and nominate these GDG members. Once all members have agreed to participate, the GDG can become functional.

Composition guideline development group
Diversity is an essential feature of a GDG and its exact composition should be tailored to the guideline topic and reflect the range of stakeholders involved. It may be helpful to consult clinical experts in the field to ensure that all relevant expertise and experience are represented for an objective evaluation. A GDG should comprise at least:

- content expert(s)
- non-expert clinician(s)
- allied health care provider(s) and an
- ESHRE research specialist.

In addition, patients or their representatives may be eligible members and, if necessary, the GDG can be expanded with, for instance, an economist, pharmacist or technical expert. However, industry representatives are excluded from membership. A maximum of 5 to 8 GDG members are recommended in addition to the chairperson. Simultaneous membership of more than one GDG is generally not recommended.
For GDG composition the following points should be considered:

- geographical balance; representatives from all parts of Europe and
- gender balance.

In general, a GDG cannot be composed of members from one ESHRE SIG alone. In particular in the case of a narrow guideline topic, a representative from a related society might be considered for membership of the GDG, but, in the case of a joint guideline development with partner organizations, the Executive Committee must approve this proposal.

Patient participation

Patients or their representatives, because they may have different perspectives on healthcare processes, priorities, and outcomes from those of health care professionals, can hold per guideline one ESHRE GDG membership. Patient involvement in guideline development is therefore important to ensure reflection of their needs, concerns and preferences. Patient needs and preferences should be for each guideline at least be considered with respect to:

- information
- communication
- accompaniment
- health care content
- health care organization
- shared decision making and
- self-management.

For the identification of patients' views the following methodologies can be applied:

- literature search
- patient (organization) consultation e.g. by (focusgroup) interviews
- guideline review by patients or their representatives.

Responsibilities guideline development group

A GDG chair is appointed for a period of four years and should be a respected content expert, with good team-working skills and awareness of the group's skill mix. To ensure that the GDG functions effectively and achieves its aims all members conform with the following:

- acceptance and tolerance of varying viewpoints
- open discussions
- evidence trumps opinion
- shared workload

- definition of any areas of confidentiality
- rejection of publishing without group's agreement
- training in guideline development (Campus workshop Nijmegen)
- commitment to attend all the meetings
- declaration of any conflict of interest.

A two-day workshop on evidence based guideline development is recommended for all GDG chairpersons and members. Within this training instructions are given about the methods to be used in the different steps of guideline development (see figure 1.1) to increase and equalise the level of guideline development expertise within a GDG.

If a GDG member cannot attend two meetings in a row, he/she may be asked to stand down by the chairperson. New members should usually not be added to the GDG once the development process is under way. Additionally needed expertise or the replacement of a GDG member should be discussed with the Deputies of the SIG SQUART.

In addition, because ESHRE aims to ensure objectivity and independence in its European guidelines, the guidelines are developed without external funding. In addition, all GDG chairpersons and members, have to provide disclosure statements of all potential conflicts of interest and confidentiality (see appendix B and C). The Deputies of the SIG SQUART decide if a potential conflict of interest could have an impact on the reliability of the guidelines' content. The disclosure form must be updated if any individual changes occur during the guideline development process.

Steps & Tips

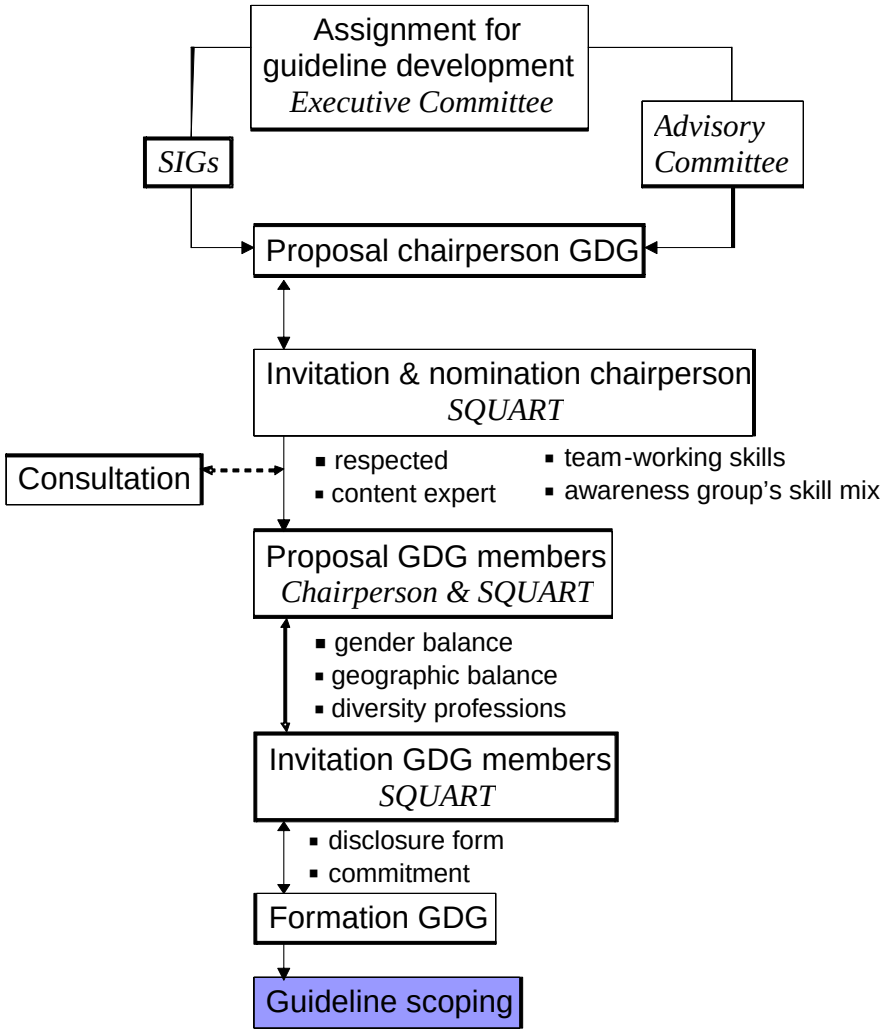

Figure 3.1 Schematic stepwise guideline development group formation

- Finalize the selection and formation process within 2 months
- Record the composition of the GDG (names, professions, conflicts of interest and represented organizations) within the guideline
- Record within the guideline that its development was without external funding

Chapter 4

Scoping the guideline

The first GDG meeting should be used to begin scoping the guideline; defining the overall objectives of the guideline (e.g. potential impact and benefits), the patients and target users to whom the guideline is meant to apply and its relation to other (ESHRE) documents. One of the guides within this process can be a bottleneck analysis; insight into the obstacles of reproductive health care delivery may help to focus on clinical situations with most improvement potential and to facilitate the applicability of a guideline.

Scoping procedure

In general a scoping procedure will start with a brainstorm session performed by the GDG. An additional preliminary literature search, performed by GDG members, is conducted to determine the scope of the guideline as appropriate. This scoping phase can also be used to inventory by consultation the target users' and patients' expectations of and preferences for this guideline. Methodologies to be used for consultation are, for instance, individual or focus group interviews, but also written surveys can be used. After outline consensus on what is within and outside the scope of the guideline, its scope can be described according to a checklist (appendix D). The items to be described are:

- overall purposes of the guideline – for example: (cost-)effective care
- target users to include/exclude – for example: embryologists, gynaecologists
- patient condition to include/exclude – for example: type of diagnosis, duration of subfertility
- patient population to include/exclude – for example: age restrictions
- healthcare setting to include/exclude – for example: legislation, reimbursement system, secondary or tertiary care
- diagnostics to include/exclude – for example: semen analysis, laparoscopy
- interventions/treatments to include/exclude – for example: surgical treatment, psychological treatment, gamete donation, lifestyle advice
- outcomes to include/exclude – for example: pregnancy and complication rates
- patient preferences – for example: mild ovarian stimulation or twin pregnancies
- relation to other (ESHRE) documents – for example: other ESHRE guidelines, the European Tissue Directive and Ethics and law task forces.

Subsequently, the guideline scope must be evaluated based according to the following points:

- valid completeness
- European view
- feasibility within the timescale.

Once the scope has been signed off the GDG begins to formulate the key questions as the basis for literature searching. After scoping the timelines for guideline development should be set.

Health economics

Guidelines are generally meant to provide clinically relevant information outside the context of costs and reimbursement. If cost issues must be included, the GDG members should limit the scope to previously published analyses and not perform any new economic analysis.

Steps & Tips

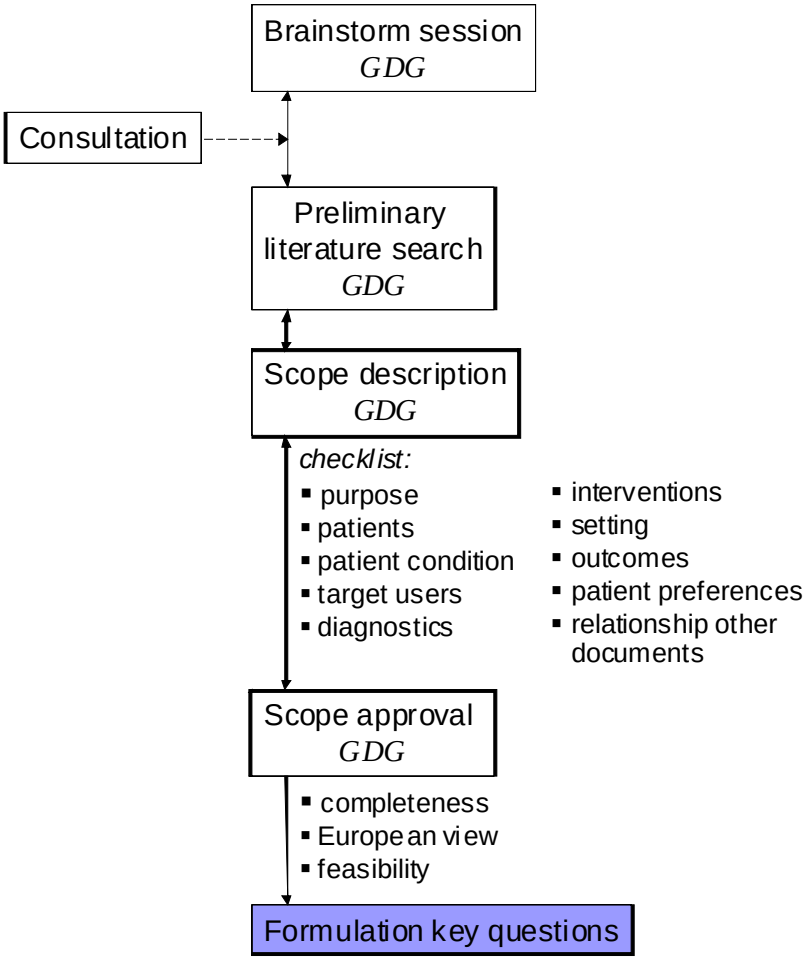

Figure 4.1 Schematic stepwise guideline scoping

- Record the scope description's items within the guideline
- Guideline scoping provides the opportunity for patient consultation
- Set timelines for the whole guideline development process

Chapter 5

Formulating key questions

Effective and efficient guideline development involves asking and answering key questions. Thus, the guideline's scope is divided into different clinical stages (e.g. diagnosis, prognosis, treatment) and for each stage key questions are defined. This chapter describes how well developed key questions are formulated, agreed and incorporated within the guidelines. Key questions should be clear, focused and closely define the boundaries of the topic. They are important both as the starting point for the subsequent systematic literature review and as a guide for the development of recommendations.

Developing key questions

A helpful framework to format key questions systematically is the PICO framework. This framework divides each question into four components:

- Patients/population
- Interventions
- Comparisons
- Outcomes.

A checklist can help to define these four PICO components (appendix E).
For the patients/population component, the definition of age groups and particular diagnostic, ethnic or social groups can be recommended. For defining the intervention component clearly and precisely - for instance diagnostic tests - risk exposure or an artificial reproductive technology must be specified. For the comparison component, it should be decided if the chosen intervention will be compared with placebo, no treatment or an alternative intervention. Finally, it is important to specify the outcome(s) of interest and by which factors it may be influenced. For instance, for key questions relating to diagnosis the outcome component of the PICO framework must be focused on accuracy, reliability, safety and acceptability to the patient.

Selecting key questions

Around 15-20 questions would be a reasonable number of key questions for guidelines taking 18-24 months to develop. It may be necessary to divide a guideline topic requiring more questions into subtopics or more guidelines.
During the final selection of key questions within a guideline the overall guideline outline should be kept in mind; each step of a clinical scenario needs to be addressed in a logical sequence. For example:

- diagnostics
- treatment options
- monitoring options
- potential benefits/risks
- outcome
- prevention
- information provision

The GDG selects the definitive key questions by a consensus approach (see if appropriate Chapter 6).

Steps & Tips

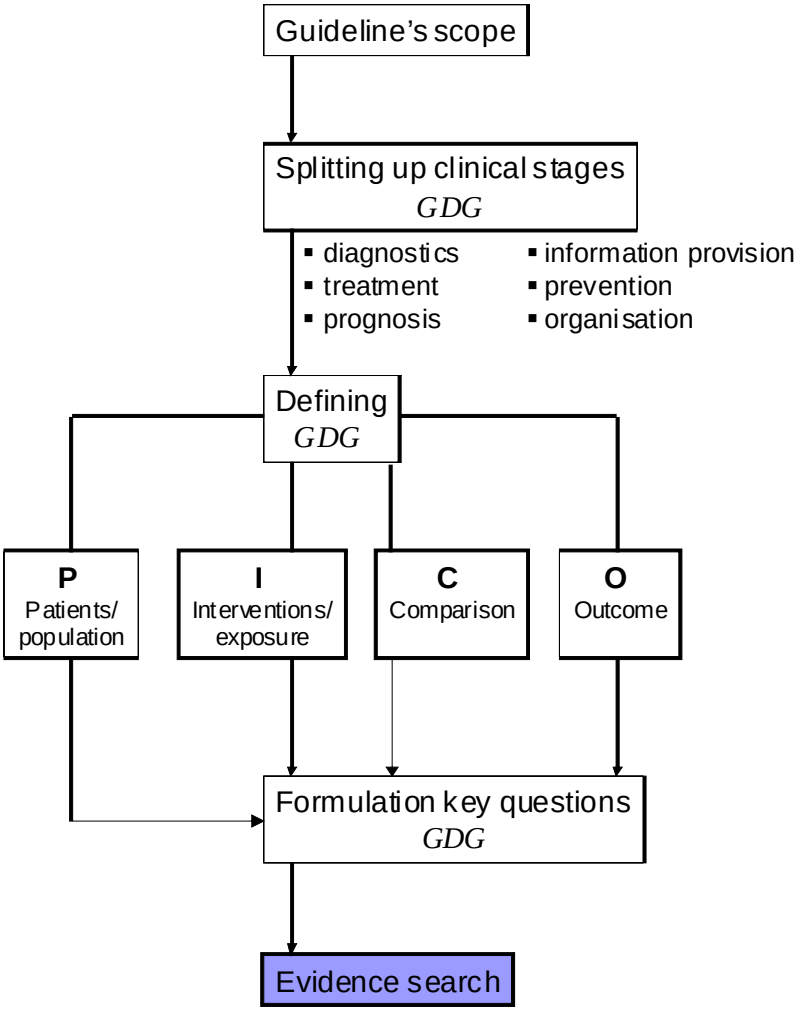

Figure 5.1 Schematic stepwise key question formulation

- Define key questions in such a way that answering the question gives the opportunity to make a recommendation
- Select no more than 15-20 key questions
- Describe the selected key questions literally within the guideline
- Think of formulating key questions in addition to health benefits - and on side effects and risks

Chapter 6

Identifying evidence

The identification and selection of evidence is an essential step towards answering the key questions. The first step is to look for existing guidelines addressing the same question(s).

Secondly, in order to perform an evidence search the key questions should be translated into key words or search terms. The evidence search itself should be gathered in a systematic process to avoid or minimize bias. Finally, from the identified literature the relevant evidence should be selected for summary and evaluation.

Existing guidelines

The evaluation and/or adaptation of (an) existing guideline(s) may be more appropriate than developing a new guideline. To check the presence of existing guidelines the following websites are recommended:

- American Society for Reproductive Medicine (www.asrm.org)
- Guidelines International Network (www.g-i-n.net)
- National Guideline Clearinghouse (www.guideline.gov)
- National Health and Medical Research Council (www.nhmrc.gov.au)
- National Institute for Clinical Excellence (www.nice.org.uk)
- New Zealand Guidelines Group (www.nzzg.org.nz)
- Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)
- World Health Organization (www.who.int).

All guidelines found in the search must be evaluated by using, for instance, the AGREE Instrument[15] and shown to have followed an acceptable methodology before they can be considered for use. For this adaptation procedure the ADAPTE methodology is recommended[16].

Literature search

According to the Institute of Medicine, literature searching is the key step in developing valid guidelines, because incomplete or biased literature evaluation can lead to inappropriate recommendations. The search for relevant research should be comprehensive, based on explicit criteria, and the validity of the results should be judged in a rigorous and reproducible fashion[17].

The ESHRE stepwise methodology (figure 6.2) is based on the methodology used by the Scottish Intercollegiate Guidelines Network (SIGN) and the American

College of Cardiology Foundation and American Heart Association (ACC/AHA), which focuses on the best available evidence to address each key question. A set of standard search filters is used for identification in the following order:

- systematic reviews/meta-analyses
- randomized controlled trials
- non-randomized studies
- observational studies
- case reports/opinion documents.

Where adequate published systematic reviews exist, additional searching may be limited to updating, covering the time period since the review was conducted. If no meta-analysis or systematic review exists, the publication type can be expanded to include randomized controlled trials and so on. Furthermore, the following rules are also recommended:

- only peer reviewed published literature should be considered
- the use of abstracts should be avoided except in very rare instances
- unpublished clinical trials should be avoided to support any recommendation.

The GDG should establish in advance a set of basic selection criteria (e.g. duration of a follow-up period, the primary outcome measure, age limits). The process for evidence identification should also be repeatable and transparent. The search strategy, including search terms, should therefore be documented and stored. This also simplifies running the search strategies to check the validity of a guideline.

An ESHRE research specialist embedded within an academic and clinical environment will conduct the literature searches, but GDG members are welcome to conduct their own literature searches. To put the ESHRE research specialist in place, GDG members are asked to complete the ESHRE literature search request form (appendix F).

Literature searching includes at least the following online databases:

- MEDLINE/PubMed
- Cochrane Library.

However, it is expected that in most cases the search will also cover additional sources (e.g. NHS Economic Evaluations Database (NEED), psycINFO and Embase) specific to the topic under review.

The searches are limited to:

- English language
- human subjects
- defined time frame; searches in a guideline update are limited to the period following the last publication of the guideline; if a suitable systematic review or meta-analysis is identified, an update search is limited to the time period following the reported search cut-off date.

Although the research specialist performs a preliminary level of sorting based on title and abstract, the clinical expertise of GDG members is necessary to carry out the definitive sifting of the search output. In practice, a single search does not cover all the questions addressed within a guideline. Different questions may be best answered by different databases, or may rely on different levels of evidence.

Following evaluation of the first search results the key questions may be redefined and subsequent searches focused on the most appropriate sources and study types. As a result, the assembly of evidence is a stepwise and iterative process. The followed strategies are published on the ESHRE website as part of the supporting materials for a guideline. The definitive evidence selection is based on the full-text documents.

Role of qualitative research

Qualitative research methods are increasingly used. However, at present there is no established mechanism for incorporating such studies in an evidence based guideline development. Nevertheless, the use of qualitative studies can help identify issues of concern to patients. A qualitative approach to complement trial data in the collection of information on patient preferences and the values placed on outcomes would perhaps help bridge the gap between scientific evidence and clinical practice.

Consensus

GDG members need to make collective decisions throughout the entire development of a guideline. Such consensus includes generating key questions, agreeing the best evidence to answer them, and formulating recommendations. There are many different approaches to making group decisions and reaching consensus – but there is no blueprint about which approach should be used. Resources for consensus development methods can be found in the systematic review by Murphy and others[13]. The most commonly used consensus development methods are the:

- nominal group technique
- Delphi survey
- RAND/UCLA appropriateness method.

Steps & Tips

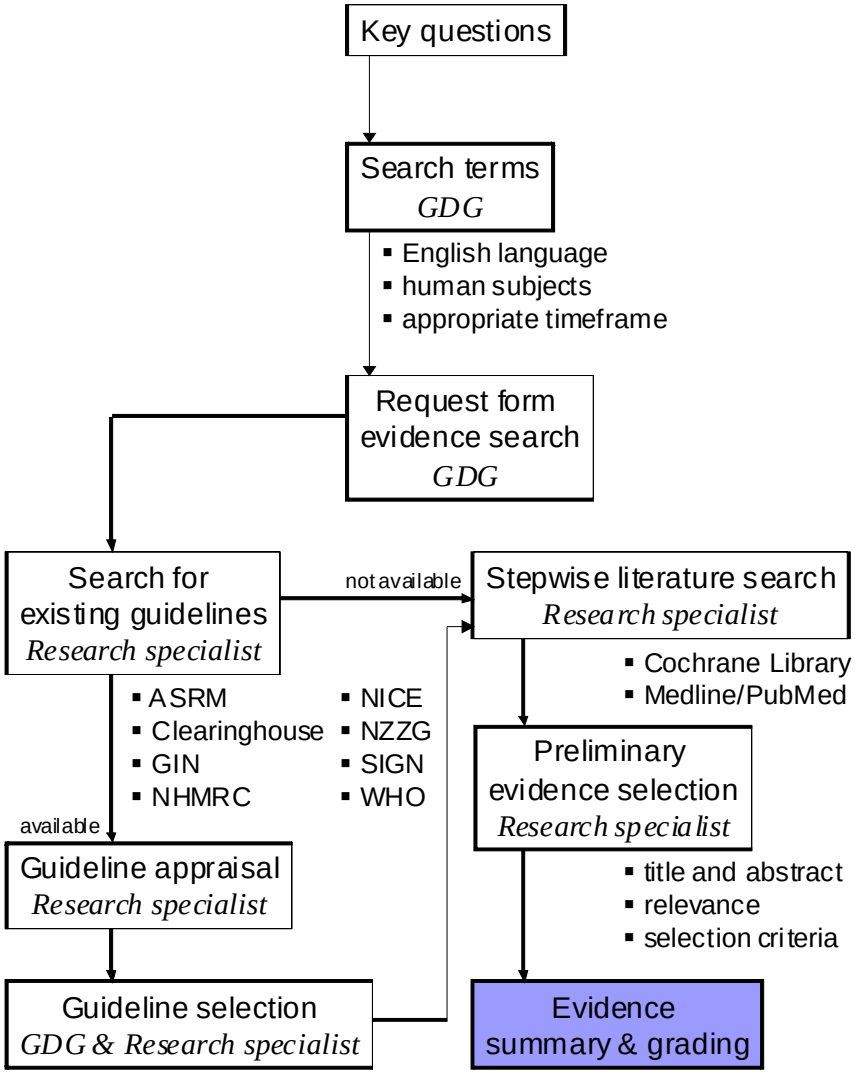

Figure 6.1 Schematic stepwise evidence searching

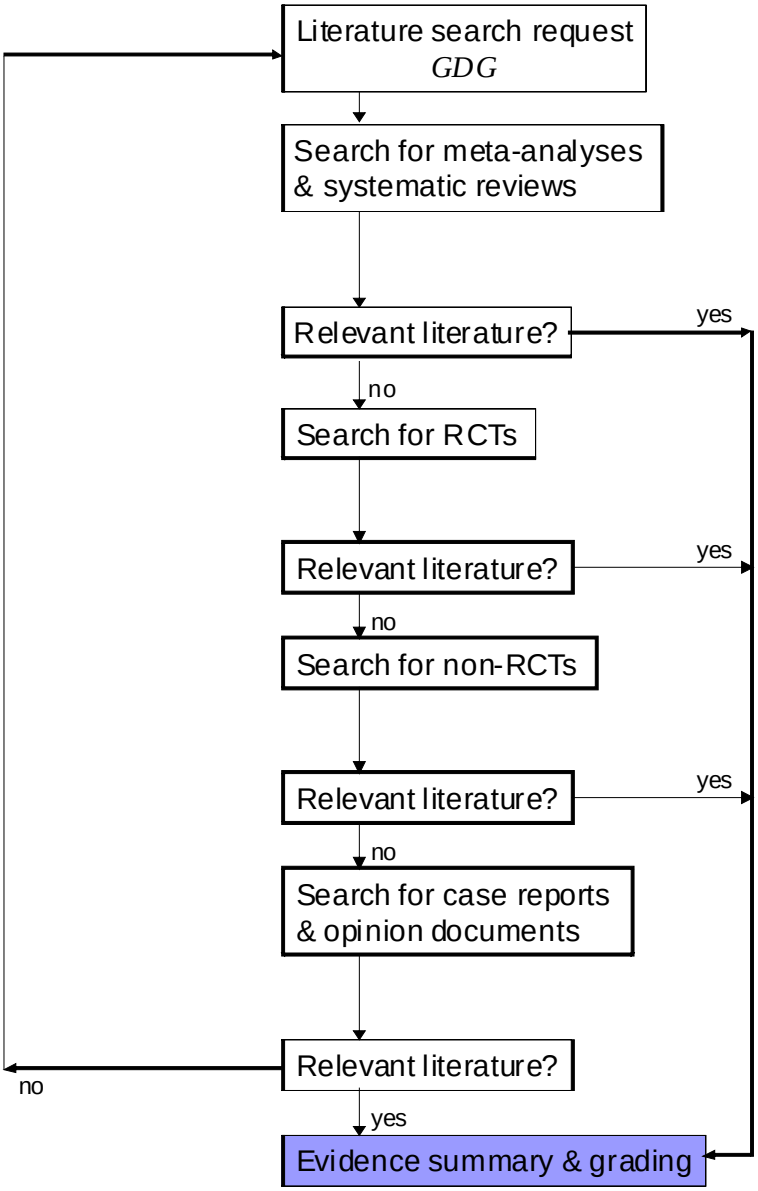

Figure 6.2 Schematic stepwise literature searching performed by the ESHRE research specialist

- Document and store the search strategies used
- Record how patients' perspectives are included within the evidence search
- Found evidence gaps can be used for future research goals

Chapter 7

Summarizing evidence

Studies identified during the stepwise literature search should be reviewed to identify the most appropriate data for answering the key questions and ensure that recommendations are based on the best available evidence. This process should be explicit and transparent and should be carried out through a systematic review process. This involves four major steps: selecting relevant studies; assessing their quality; synthesising the results; and grading the evidence.

Selection evidence

Papers are initially selected according to title and abstract by the ESHRE research specialist (figure 6.2).

First, the titles of the retrieved citations are scanned and those that fall outside the topic of the guideline are eliminated. Next, a quick check of the remaining abstracts identifies further papers not relevant to the key questions, and these are also excluded. The remaining abstracts are investigated if they fulfil the selection criteria agreed by the GDG. If no or incomplete information is available in the abstract, the full text is assessed in consideration of the next step: assessment of the quality of each study to ensure its validity and applicability. The study selection process is clearly documented and details the applied inclusion criteria.

Quality assessment

Quality assessment of the selected evidence is necessary to ensure that recommendations are based on the highest quality evidence available. Quality assessment is performed on each individual study. However, if the study is a meta-analysis or systematic review quality assessment should be performed on the meta-analysis or review itself and not on the studies included. To minimize any potential bias, independent assessment by two reviewers is desirable. In this way quality assessment is carried out according to checklists by the ESHRE research specialist and the GDG member responsible (appendix G). The checklists are based on the key domains defined by the Agency for Healthcare Research and Quality (AHRQ) to rate the strength of scientific evidence[18]. Differences in assessment should be discussed to encourage consensus. In extraordinary cases a third independent person might be asked for assistance. A study should be rejected if its quality is assessed as low. If no better evidence can be found, the study might be considered as C level evidence, comparable with expert opinions.

Factors that warrant assessment are those related to:

- applicability of findings and
- study validity.

Applicability, which is also known as external validity or generalisability, is related to the definition of the components (PICO) of the formulated key questions (chapter 5). Comparison of the available articles with the defined PICO components guides the selection of papers with the relevant evidence.
The validity of a study is the extent to which its design and conduct are likely to prevent systematic errors, or bias. There are four potential sources of systematic bias in healthcare trials:

- selection bias – randomization (Patients/population)
- performance bias – blinding (Intervention)
- attrition bias – handling participant loss (Comparison) and
- detection bias – outcome assessment (Outcome).

One of the most important factors leading to bias and distorted treatment comparisons is patient assembly. An appropriate method for preventing foreknowledge of treatment assignment is crucial for any study. True randomization is administered by someone who is not responsible for the recruitment of study subjects. Thus, studies are for the selection bias judged on the quality of the used allocation concealment methodology.

Performance bias refers to systematic differences in the provision of care to the participants in the intervention and control group. Those providing and receiving care can be 'blinded' to protect against unintended differences in care. Judgment for performance bias includes three questions:

- Were the recipients of care unaware of their assigned intervention?
- Were those providing care unaware of the assigned intervention?
- Were persons responsible for assessing outcomes unaware of the assigned intervention?.

Attrition bias, also known as exclusion bias, alludes to systematic differences in the approach to handling the loss of participants (e.g. withdrawals, dropouts, protocol deviations) in the two study groups. This may have great potential for biasing results.

Detection bias is a systematic difference between two study groups in outcome assessment. Trials which blind those assessing outcomes are logically less likely to be biased than trials that do not.

A validity assessment of a study is not always possible because of the inadequate reporting of papers. Therefore, the four sources of potential bias are rated as "met", "unmet", or "unclear". These four scores are summarized as a study rating with a range of low to high risk bias. This validity assessment can be used as a:

- threshold for study inclusion (e.g. meeting more than one validity criteria indicates a high risk of bias and constitutes grounds for study exclusion)
- possible explanation for found differences in study results.

The study selection procedure should be documented and include details about the applied inclusion criteria. At this point the available evidence is ready for summary.

Summary evidence
Evidence tables help to identify similarities and differences between studies. Data for inclusion within an evidence table should be extracted according to a standard template (appendix H and I). Here, key characteristics of the study population (e.g. sample size, age), intervention (e.g. follow-up period, kind of intervention), comparison (e.g. IUI versus timed intercourse) and outcome measures (e.g. effect size) are important. The evidence tables should be stored and can be published on the ESHRE website as part of the supporting materials of a guideline. Description of the study design is also important as a level of evidence.

Levels of evidence
Grading the included evidence gives the reader a quick impression of the quality of the studies included. This grading is not related to the importance of the recommendation but to the strength of the supporting evidence. In other words the higher the grading, the higher the predictive power of a recommendation; if a recommendation based on a high level of evidence is implemented, the higher the chance that the predicted outcome will be achieved.

ESHRE, as the American College of Cardiology Foundation, American Heart Association and the European Society of Cardiology, uses three levels of evidence[1,4]:

- Level A data derived from multiple randomized trials or meta-analyses
- Level B data derived from a single randomized trial or large non-randomized studies
- Level C retrospective studies, case studies or experts' opinions.

Steps & Tips

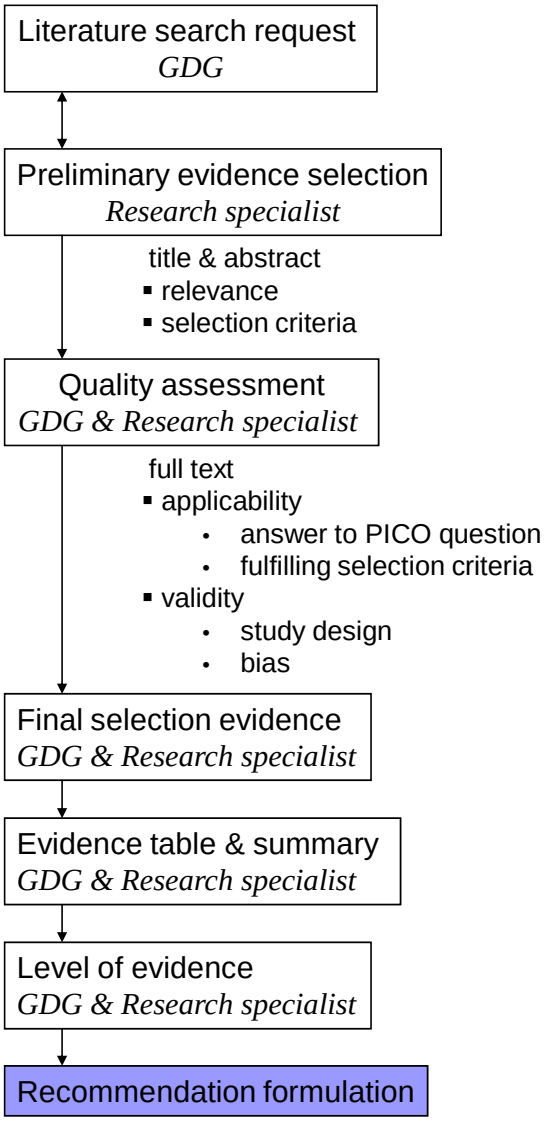

Figure 7.1 Schematic stepwise evidence summarizing and grading

- Record the set of evidence selection criteria
- Record the level of evidence
- Document and store the quality assessment of the selected evidence
- Document and store the evidence tables

Chapter 8

Developing recommendations

Once the selection and summary of evidence is complete, the available evidence must be combined and condensed into recommendations. Recommendations are statements mostly proposing a course of action. An ESHRE guideline recommendation should be a stand-alone text written in a complete sentence. ESHRE suggests standardized phrasing for recommendations, which reflect the level of evidence. Each GDG member prepares in collaboration with the research specialist his/her specific recommendations and sends them for feedback to the other GDG members. When the GDG has finally reached consensus, the draft version of the guideline can be written.

Grading recommendations

Recommendations should be graded so that standardized phrasing for ESHRE guideline recommendations can be applied. According to the GRADE system, a recommendation classification of “strong” or “weak” should be made. A “strong” recommendation reflects the GDG’s confidence that the desirable effects of recommendation adherence outweigh the undesirable effects; a “weak” recommendation indicates less confidence[19]. The American College of Cardiology Foundation, American Heart Association and the European Society of Cardiology classification systems are used to classify the recommendations definitively[1,4]:

- Class I there is evidence and/or general agreement that a given procedure/treatment is useful and effective
- Class II there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
    - IIa evidence/opinion is in favour of usefulness/efficacy
    - IIb usefulness/efficacy is less well established
- Class III there is evidence and/or general agreement that a given procedure/treatment is not useful and effective or even harmful.

Classes I & III are directly based on level A evidence. Class IIa is directly based on level B evidence or extrapolated from level A evidence. Class IIb is directly based on level C evidence or extrapolated from level B evidence. In addition, experts’ view of the GDG can be represented by good practice points (GPP).

Formulation recommendations

According to the grading classification, the following standardized phrases are recommended to formulate the guideline recommendations. See for a summary appendix J.

- Class I should
  is recommended/indicated
  is useful/effective/beneficial
- Class IIa is reasonable
  can be useful/effective/beneficial
  is probably recommended or indicated
- Class IIb may/might be considered/reasonable
  the usefulness/effectiveness is unknown/unclear/uncertain
  the usefulness/effectiveness is not well established
- Class III should not
  is not recommended/indicated
  is not useful/effective/beneficial
  may be harmful
- GPP the GDG recommends.

ESHRE guideline recommendations could stand alone and contain enough detailed information to be understandable without references to supporting material. They are written in complete sentences and should answer the key questions. In addition, the wording must be:

- unambiguous
- clearly defined
- easy to translate into clinical practice and
- agreed by the complete GDG.

A help to guarantee the formulation of such clear recommendations is the five ‘W’ rule: each recommendation should be a description about **who** does **what** for **whom, when** and in **which way**.

Possible benefits and harms should be quantified as much as possible. Any exceptions to the recommendations should be listed whenever possible.

Steps & Tips

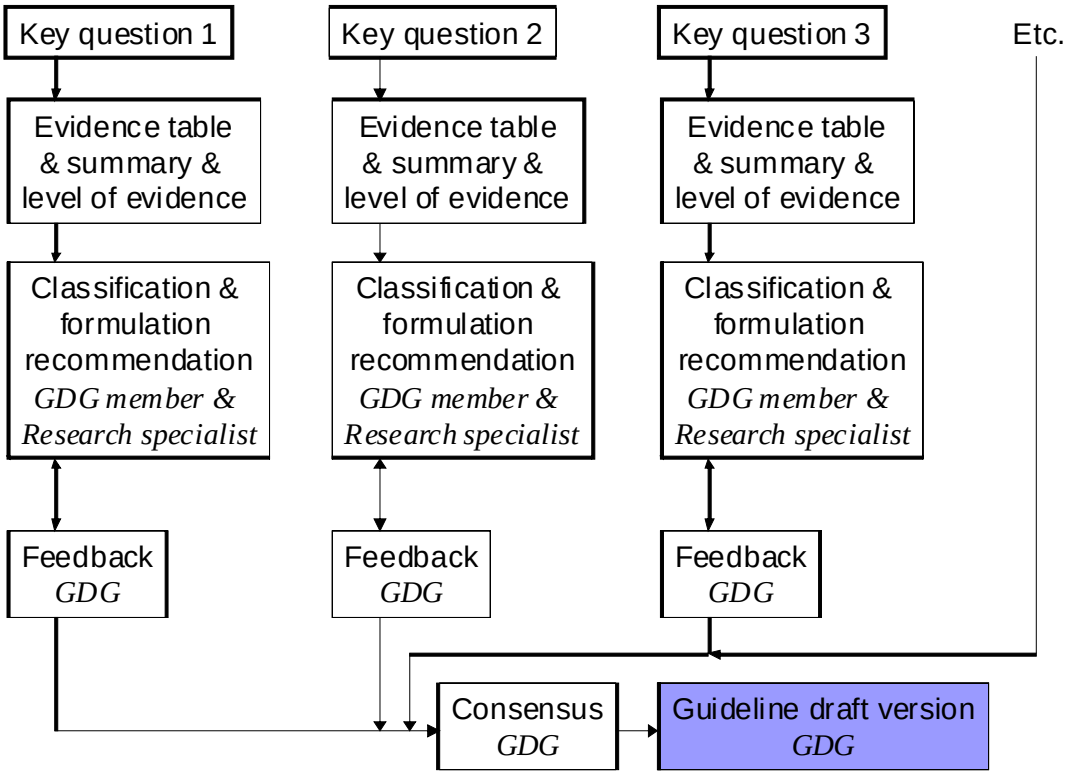

Figure 8.1 Schematic stepwise recommendations formulation

- Recommendations should be specific and unambiguous
- Use the five 'W' rule
- Record or refer to the methodology used for recommendations' formulation
- If no consensus is reached, describe the different views and options

Chapter 9

Writing the guideline

Principles for writing

Once key questions are answered and there is consensus about the guideline's recommendations, the first draft version can be written. However, writing in committee requires prior agreement about the consistent use of terminology and writing style. ESHRE guidelines should be written in English and within a European scope. Furthermore, they should be comprehensive and flexible in order to allow adaptation to diverse settings and circumstances of clinical practice.

The use of paragraphs and headings are recommended to facilitate readers' navigation. Moreover, the use of tables, illustrations, figures and algorithms is encouraged. For guideline uniformity an ESHRE guideline is written according to an established structure.

Guideline structure

In general, an ESHRE guideline consists of five main parts in the following order:

- guideline background
- general introduction
- summary
- key question related part and a final
- general part.

The guideline's background describes the guideline development and details:

- guideline development group membership
- funding
- potential conflicts of interest
- review panel
- testing process if appropriate
- used guidelines' manual version
- guideline's scope based on its:
  - purpose
  - target users
  - target population (definitions and classifications if appropriate)
- patient involvement.

The general introduction is usually written by the guideline development group's chairperson and considers the following clinical core elements if appropriate:

- epidemiological data of the clinical condition in question by e.g.:
  - European prevalence/incidence

    - natural history
- probable diagnostics and their sensitivity and specificity
- treatment or monitoring options
- probable outcomes with different interventions including a balance of benefits against risks.

These outcomes can be specified in physical (e.g. pregnancy or OHSS rate), social (e.g. divorce rate or financial problems) or psychological function (e.g. depression rate).

The summary section contains a short guideline overview combined with a list of all recommendations possibly supported by algorithm(s).

For the key question related part the guideline development group determines a logical order for reporting the total collection of key questions with their recommendations. One such method is to follow the patients' pathway, starting with the clinical evaluation (e.g. symptoms, risk factors) followed by the diagnostics, treatment options, follow-up, complications, information provision etc.

Per key question the following items are reported:

- the key question itself
- an explanatory text, summarizing the selected evidence
- the recommendation(s) including grading
- the involved references.

The explanatory text also contains information about expected exceptions – circumstances in which a recommendation would not apply – or potential risks, barriers for application, needed support services, needed training or cost implications. In the case of non-consensus, practice statements about the different schools of thought should be recorded. Furthermore, the explanatory text gives room for considerations from patient, ethical or legal perspectives.

The final general part provides comment on the guidelines':

- dissemination (e.g. existence of additional tools)
- relationship with other existing guidelines or ESHRE documents
- update proposal
- key priorities for implementation and
- disclaimer.

There is also room in this final part to describe gaps in current scientific knowledge for future investigation.

Disclaimer

A legal disclaimer should be included in all guidelines. The following text is suggested:

> "This document is a general guide to appropriate practice, to be followed only subject to the medical practitioner's judgment in each individual case. The guideline is designed to provide information to assist decision making and is based on the best information available at the date of publication".

Steps & Tips

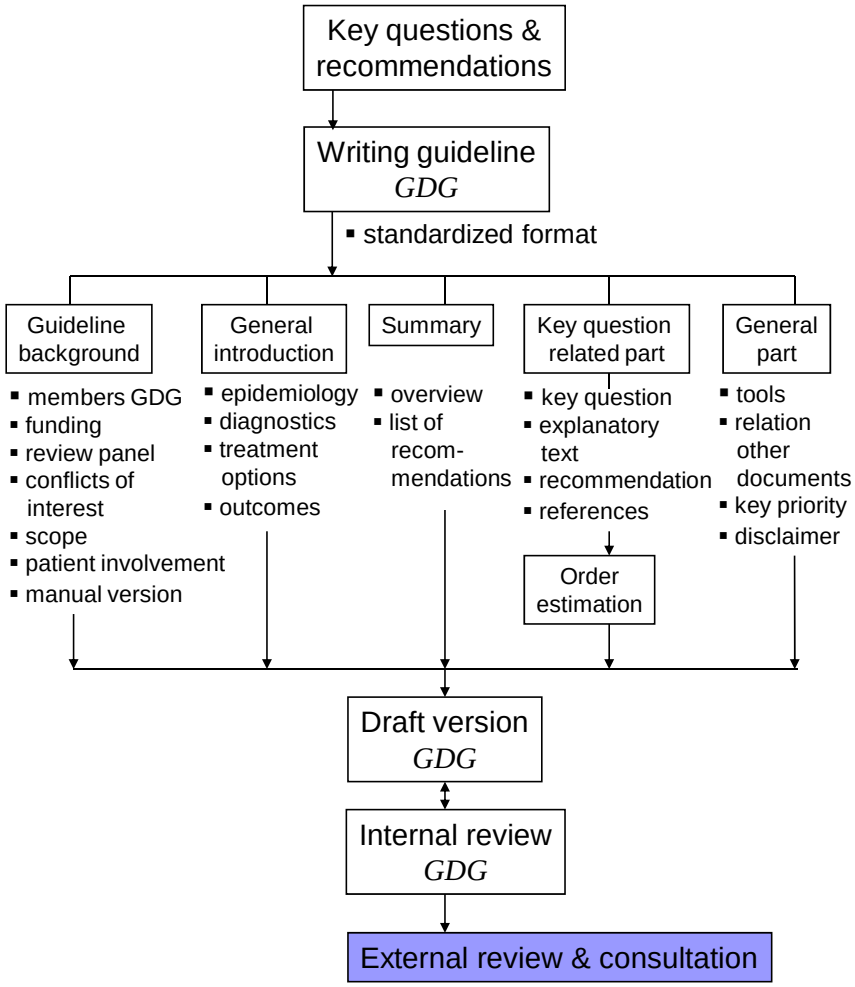

Figure 9.1 Schematic stepwise guideline writing

- Check if recommendations answer the key questions
- Use the AGREE Instrument (www.agreetrust.org) as a checklist
- Link the recommendations explicitly to the supporting evidence
- Present the different management options clearly
- Present if appropriate expected exceptions for recommendation application

- Facilitate recommendation identification (e.g. bullets, numbering, boxes)
- Discuss potential barriers in applying the recommendations
- Consider potential cost implications of applying the recommendations

Chapter 10

Consulting stakeholders

The final stages of guideline development involve review by future users and approval by the parties involved, the SIG SQUART's Deputies and finally the ESHRE Executive Committee. Within this phase the adequacy of the guideline document is evaluated, especially for its methodological quality, its clinical content and its applicability.

Review procedure

The review phase starts with a review of the guideline draft by several stakeholders. Their consultations concern in particular the guidelines' comprehensiveness, the accuracy of evidence interpretation and the acceptance of recommendations.

Firstly, all members of the ESHRE Advisory Committee, the involved SIGs and some patients' representatives (lay reviewers) are invited to review the draft. Secondly, the draft is web posted and all ESHRE members are invited to review. Interested reviewers must disclose any potential conflicts of interest and confidentiality (appendix B and C) and submit their review comments within six weeks. Following this procedure results in an addition to the reviewers' list. All reviewers are asked to select from all proposed recommendations a maximum of five, which should have priority for implementation.

For adapted (parts of) clinical guidelines the ESHRE draft guideline should be also sent for review to the original developers of those recommendations used.

An additional open meeting at the ESHRE annual meeting is also an option for review. This provides the opportunity to present preliminary conclusions and draft recommendations to a wider audience and to hear valuable suggestions for additional evidence or alternative evidence interpretation. Because participation in such a meeting generates a sense of ownership across geographical and disciplinary boundaries, the organization of such a meeting might accelerate the internal consensus process, the review procedure and final implementation.

A draft guideline can also be pilot tested before a wider launch. This step can detect problems in formatting, usability and acceptance.

After reviewing the GDG integrates the reviewers' comments and sends the revised version along with a comments processing report for a methodology check to the SIG SQUART's Deputies. This methodology check is based on the principles outlined in this guidelines' manual, the validated AGREE Instrument and the comments processing report. This check ensures quality and minimal bias in the guideline development process (see appendix K).

The comments received from reviewers are tabulated and discussed in the comments processing report. Changes must be made with the agreement of the whole GDG and noted within this report. If no change is made, the reasons for this should be also recorded. This comments processing report is posted on the website once the relevant documents are published.

Each member of the guideline development group is then asked formally to approve the final guideline for publication.

Final version & authorization

After completion of all revisions English language reviewers and proofreaders (and possibly lawyers) are called upon when necessary. Final approval is given by the ESHRE Executive Committee.

Steps & Tips

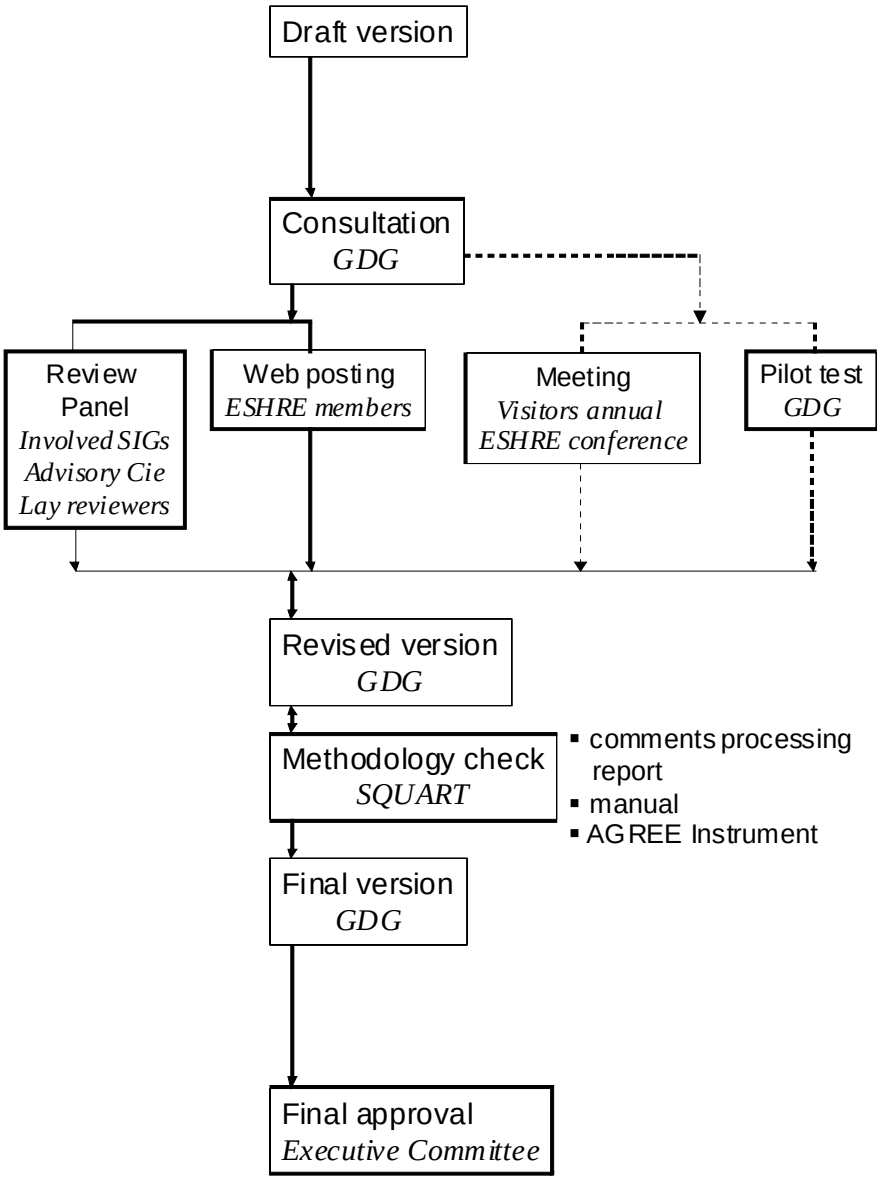

Figure 10.1 Schematic stepwise guideline review and consultation

- Pilot the guideline among target users and record this within the guideline
- Organize at an early stage of writing an open meeting for feedback from experts
- Use the reviewing and piloting phase as an opportunity to advertise the existence of a new guideline

Chapter 11

Disseminating the guideline

Dissemination of ESHRE guidelines is considered as a continuation of the work of the GDG and involves making guidelines accessible, advertising their availability, and distributing them widely. Guidelines are (most) effective if their dissemination and implementation are carefully considered and vigorously pursued. If not, the time, energy and costs devoted to their development are wasted and potential improvements in reproductive health care are passed.
A range of dissemination strategies can be effective[20], for instance the:

- use of short summaries
- promotion of guideline's development/existence
- publication in professional journal(s)
- publication on the Internet and links on related websites
- use of common communication structures.

Currently there is too little evidence to support decisions about which guideline dissemination strategy is efficient under which circumstances. In general, the use of multi-faceted dissemination strategies is recommended.

Standard publications
The standard dissemination procedure for all ESHRE guidelines comprises publishing (3 steps) and announcement (6 steps).

For publication the full-length version and short summary are (1) posted on the ESHRE Website and (2) the GDG's chairperson sends the ESHRE guideline, formatted to journal style, to the Editor-in-Chief of Human Reproduction. Finally (3), a procedure for inclusion on the National Guidelines Clearinghouse's Website is followed after the release of every new document.

New selected topics for guideline development will be presented (1) as an annual announcement in "Focus on Reproduction". An announcement reporting the release of a new ESHRE guideline is (2) published as a newsflash on the ESHRE website's homepage and (3) as a news item in the monthly digital ESHRE newsletter. Moreover, (4) all participants in the annual ESHRE meeting will be informed about the development and release of new guidelines during a specific guideline session. Fifth (5), all related National Societies are separately informed about the guideline release but are also formally asked if they would like to endorse it. They are asked to encourage local implementation by, for instance, translations or condensed versions, but they are also offered a website link to the original document. Finally (6), all appropriate remaining stakeholders - for

instance, European policy makers, patients societies and industry representatives - will be separately informed.

Additional options

Distribution of guidelines alone has been shown to be ineffective in achieving change in practice; guidelines are more likely to be effective if they are disseminated by a strategy based on barrier research, by an active educational intervention or by patient-specific reminders[20]. However, the extent of potential clinical benefits and resources required to introduce guidelines - and the likely benefits and costs as a result of any provider's behaviour change - need to be considered carefully before developing additional tools. The efficiency of a dissemination strategy is best evaluated in the presence of different barriers and effect modifiers. See for more detail chapter 12.

Two more accessible options are the development of algorithms and patient information.

An algorithm is a flow chart of the clinical decision pathway described in the guideline, in which process steps and decision points are linked by arrows. Patient information summarizes the recommendations in the ESHRE guideline in everyday language. It aims to help patients understand the guideline's recommendations and facilitates decision-making. Moreover, the patient information may be used by hospitals or patient organizations for developing their own information leaflets.

Tips

- Support the guideline with application tools and record those within the guideline

Chapter 12

Implementing and Evaluating

Guidelines do not implement themselves[10]. Local ownership of the implementation process is crucial for changing practice. ESHRE is responsible for the development of European guidelines and their implementability, but not directly for their implementation into local practice[21]. Nevertheless, the identification of barriers to guidelines' acceptance is one of the first steps of an implementation process and has ideally been part of the guideline developmental phase[22]. Instruments like The Guideline Implementability Appraisal instrument

(ycmi.med.yale.edu/GLIA) can be helpful for identifying obstacles to guideline implementation[23].

There are different types of barriers to guideline implementation[22,24,25]:

- internal to the guideline itself
- factors related to the individual care providers (e.g. attitude and skills)
- factors related to the (social) setting (e.g. patients' and colleagues' characteristics) and
- external factors related to the system (e.g. reimbursement).

After the determination of factors affecting guideline adoption, the currently recommended approach is to plan a targeted intervention. However, there is no specific guidance available for translating identified barriers into tailor-made implementation interventions[26]. Each implementation strategy is effective under certain circumstances, and a multifaceted approach is more likely to succeed than a single approach. Evaluation of such complex interventions is therefore important and mostly undertaken by investigators with research funding[27]. Focussing on individual recommendations rather than on the guideline as a whole makes the implementation initiative more manageable. Criteria reflecting one or more of the six quality domains defined by the Institute of Medicine (safety, effectiveness, patient-centredness, timely, efficiency and equitability) can help to prioritize guideline's recommendations for this purpose[28].

At an appropriate time after dissemination and implementation an evaluation is necessary for insight into the impact of the guideline. Such an evaluation consists of several components, namely an assessment of:

- guideline dissemination
- change in practice performance
- change in health outcomes
- change in consumer's knowledge and understanding
- economic consequences.

Practice performance is usually measured by a clinical audit and indicators. The frequently used definition for an indicator is "a measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality of care provided"[29].

Guideline endorsement

An important factor facilitating guideline implementation is endorsement by professional groups; endorsement indicates that the guideline has been examined closely by clinicians. Endorsement of ESHRE guidelines is always sought from relevant National Societies by informing their presidents. A list of the National Societies having officially endorsed a certain guideline is posted on the ESHRE website.

ESHRE gives National Societies the optional right to translate, adapt and publish the translated guideline in their own national journals. All costs of carrying out these rights and of translating the guideline are for the National Societies. Any financial compensation received from third parties for this procedure must be

communicated to ESHRE (SIG SQUART) directly by the Board of a National Society.

The guideline translation must be an exact translation of the English parent version and shall consist of the full-length text and illustrations without alteration, abridgement or supplement. The validation of a guideline translation is the responsibility of the National Society; ESHRE will not accept any liability in this respect. For reasons of consistency only one translation of a certain ESHRE guideline in any given language is accepted by ESHRE. The translated document should say in its (sub)title that it was translated from the ESHRE guideline and should contain the names of the GDG members of the parent document. ESHRE retains the copyright on the full-length guideline version, their translations and all their derivative products in all formats. Therefore, National Societies must obtain prior written agreement from ESHRE in order to translate, adopt and publish ESHRE guidelines. ESHRE reserves the exclusive right to publish the first edition of all ESHRE guidelines and post its translation on the ESHRE Website. National Societies must secure copyright protection in their own country.

Tips

- Discuss potential barriers in applying the recommendations within the guideline
- Facilitate recommendation identification (e.g. bullets, numbering, boxes)
- Present review criteria for monitoring and/or audit purposes others than outcome measurements like pregnancy or complication rates

Chapter 13

Updating the guideline

Guidelines should be kept up to date. All ESHRE guidelines carry a statement indicating that they will be considered for revision four years after publication[30]. Guideline updates focus on substantive changes to recommendations rather than editorial changes to the document. After guideline publication the ESHRE research specialist will undertake searches every two year for new evidence, using versions of the original search strategies and compares with the GDG's chairperson, the current guideline recommendations with the latest data. It is then discussed whether an ESHRE guideline requires a complete/partial update or not. In case of doubts the entire GDG may be surveyed to determine whether the

guideline (or sections within the guideline) needs updating. A guideline may require updating because of changes in[31]:

- availability interventions
- considered outcomes
- evidence on existing benefits and harms of interventions
- availability resources.

A full revision of a guideline occurs when there:

- have been at least two previous updates and/or
- is enough new evidence that a significant number of the recommendations need to be revised or
- there is a compelling reason to change the scope or focus of an existing guideline.

For a full revision the application procedure and renewed recruitment of GDG members will follow the usual process described in this manual.

In exceptional circumstances, significant new evidence may emerge that necessitates an unscheduled partial update of a guideline; one or more recommendations in the guideline need changing in an important way. Updated guidelines are also subject to consultation and will follow the usual validation process.

Tips

 Refer to the procedure for guideline updating

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Appendices

Appendix A

Application form

1.	Who is/are the contact person(s)?
2.	Which ESHRE Special Interest Group(s) is/are involved?
3.	What is the proposed clinical problem?
4.	Please describe the relevance of the proposed clinical problem (e.g. volume, costs and patient impact).
5.	Which outcome(s) will be addressed by the proposed guideline?
6.	Please give an indication of actual practice variation.
7.	What is/are the expected benefit(s) from the proposed guideline development and implementation?
8.	Are there already existing guidelines within the field of the proposed topic? *(screen: www.g-i-n.net, www.guideline.gov, www.asrm.org and www.nice.org.uk)*
9.	Please give an indication of the size and strength of the evidence for the proposed topic. *(screen at least the Cochrane Library)*

Signature(s) _____ Date _____

Appendix B

Disclosure form

All ESHRE guideline development group members and guideline reviewers are expected to provide complete and signed disclosure statements about all financial, personal, or professional relationships with industry, individuals, or organizations to avoid the perception of a conflict of interest. Updates should be made if changes occur during the guideline development process.

Name of the guideline development group member or guideline reviewer
Address, telephone number and e-mail address
Title involved ESHRE guideline

☐ I have no potential conflict of interest from the last 3 years to report

☐ I have the following potential conflict(s) of interest from the last 3 years to report:

- ☐ Research grant(s) from one or more companies, namely from _____
- ☐ Consulting fee(s) for e.g. services on an advisory board or legal testimony, namely from _____
- ☐ Speaker's fee(s) for instance as compensation for lecturing and travel, namely from _____
- ☐ Salary or position funding, namely from _____
- ☐ Ownership interest by stock (options) or partnership of a healthcare company, namely from _____
- ☐ Other (financial) benefit e.g. by institutional conflicts of interest in the topics or issues addressed in the document, namely _____

Signature _____ Date _____

Appendix C

Confidentiality form

As a writer or reviewer of an ESHRE guideline you have been or may be exposed to certain confidential and/or proprietary information, materials or data. It is important to the integrity of the writing process and final work that this information should be kept strictly confidential and not disclosed at any time under any circumstance.

Name of the guideline development group member or guideline reviewer
Address, telephone number and e-mail address
Title involved ESHRE guideline

I will not disclose any confidential and/or proprietary information, materials or data related to Guideline Development Group's work to any third party, but keep this information strictly confidential.

I will keep any confidential and/or proprietary information, materials or data in my possession in a safe and secure place to protect against inadvertent disclosure.

I will not use any confidential information and/or proprietary information, materials or data for any purpose other than participating in an ESHRE guideline development procedure.

Signature _____ Date _____

Appendix D

Scoping checklist

1. What is/are the overall purpose(s) of the proposed guideline?
consideration *clinical guidelines are defined as "systematically developed statements to assist care providers and patient decisions about appropriate health care for specific clinical circumstances"*
2. What are the target users of the proposed guideline?
considerations • *which clinical professionals?* • *patients?* • *paramedical professionals?* • *policy makers?*
inclusion: exclusion:
3. What is the proposed patient population?
considerations • *clinical entity, type of diagnosis?* • *duration/grade of disease?* • *age restrictions?*
inclusion: exclusion:
4. What is the proposed health care setting?
considerations • *secondary or tertiary care?* • *legislation?* • *access to care, reimbursement?*
inclusion: exclusion:

5. Should preventive intervention(s) be included in the guideline?
considerations • *life-style?* • *treatment cancellation?* • *screening?*
6. Which diagnostic intervention(s) should be included in the guideline?
considerations • *which diagnostic interventions are available?* • *what gives variation in current practice?* • *what is new or actual?*
inclusion: exclusion:
7. Which therapeutic intervention(s) should be included in the guideline?
considerations • *which therapeutic interventions are available?* • *what gives variation in current practice?* • *what is new or actual?*
inclusion: exclusion:
8. Which outcome(s) should be addressed by the proposed guideline?
considerations • *which outcome(s) is/are common to report? (long-term and short-term!)* • *which outcome is able to report practice variation?* • *what is new or actual?* • *which outcome measure is preferred by patients?* • *complications?* • *costs?*
inclusion: exclusion:

9. What prefers the proposed patient population and is this already included?
considerations • *diagnostic interventions?* • *therapeutic interventions?* • *outcome measures?* • *complications (e.g. twins, risk for OHSS)?* • *costs (e.g. twins, extra treatment cycles)?*
extra inclusion:
10. Which methodology/methodologies will be used to include patients' preferences?
considerations • *literature search?* • *consultation?(how? focusgroups, individual interviews, survey)* • *review draft version is part of the guideline development procedure*
inclusion: • review draft version exclusion:
11. What is the relation to other documents?
considerations • *other ESHRE guidelines?* • *other (inter)national guidelines?* • *ESHRE's Ethics and Law Task Forces?* • *European Tissue Directive?* • *other European legislation?*
12. Is something missing?
considerations • *information provision?* • *practice organization?*
13. Does the proposed represent an European view?
14. Is the proposed guideline feasible to develop within the timescale?
considerations if not • *splitting up?* • *more restrictions/exclusions?*

Appendix E

PICO checklist

Patients/Population:

- Which patients or population are we interested in?
- Are there subgroups of patients that need to be considered?
- How can they be best defined (e.g. cut off levels, definition inclusion- and exclusion criteria; female age < 43 years and after sperm preparation the availability of more than one million motile sperms or embryos without anucleate fragments)?

Interventions:

- Which intervention, treatment or approach should be used?
- How can it be best defined (e.g. definition inclusion- and exclusion criteria; first IVF treatment cycle or assisted hatching)?
- What follow-up period is appropriate?

Comparison:

- What is/are the main alternative(s) to compare with this intervention?
- How can it be best defined (e.g. definition inclusion- and exclusion criteria; double embryo transfer, placebo or doing nothing)?

Outcome:

- Which outcome is important for the patient?
- What does this intervention affect?
- Which intermediate or short-term outcome should be considered?
- Which risks or complications should be considered?
- Should quality of life or general health status be considered?
- Should costs be considered?
- How can they be best defined (e.g. pregnancy rate per started treatment cycle, livebirth rate per couple, dropout rate or hospital admission rate)
- Which factors may influence the outcome?

Examples:

Population	Intervention	Comparison	Outcome(s)
• female age < 36 years • unexplained subfertility > 3 years	IUI combined with ovarian stimulation	IUI without ovarian stimulation	• ongoing pregnancy rate • quality of life • costs per livebirth

Questions:
- In women younger than 36 years and having an unexplained subfertility of more than three years, does IUI combined with ovarian stimulation compared with IUI without ovarian stimulation improve the ongoing pregnancy rate?
- In women younger than 36 years and having an unexplained subfertility of more than three years, does IUI combined with ovarian stimulation compared with IUI without ovarian stimulation worsen the quality of life?
- In women younger than 36 years and having an unexplained subfertility of more than three years, does IUI combined with ovarian stimulation compared with IUI without ovarian stimulation increase the costs per livebirth?

Population	Intervention	Comparison	Outcome(s)
blastocysts after IVF	sequential media system	monoculture media system	• embryo score • implantation rate • cryotolerance

Questions:
- Do blastocysts originated after IVF and cultured in a sequential media system improve the embryo score in comparison to blastocysts cultured in a monoculture media system?
- Do blastocysts originated after IVF and cultured in a sequential media system increase the implantation rate in comparison to blastocysts cultured in a monoculture media system?
- Do blastocysts originated after IVF and cultured in a sequential media system increase the % embryos surviving freezing in comparison to blastocysts cultured in a monoculture media system?

Appendix F

Literature search request form

Each performed literature search should be documented. Therefore, please complete this form for each literature search requested.

Name of the guideline development group member			
Address, telephone number and e-mail address			
Title involved ESHRE guideline			
Key question			
Population	**Intervention**	**Comparison**	**Outcome(s)**
Keywords			
Population	**Intervention**	**Comparison**	**Outcome(s)**
Years requested			
…….…….. - …….			
Publication type(s)			
☐ all ☐ meta-analyses & systematic reviews ☐ randomized controlled trials ☐ non-randomized studies ☐ case reports ☐ opinion documents/letters ☐ others, namely ……			

Appendix G

G1 Quality assessment checklist: systematic reviews/meta-analyses

Based on SIGN methodology checklist 1: systematic reviews and meta-analyses[8] and Study quality assessment by Kahn et al.[32].

Name assessor
Bibliography (author, journal, year, volume and pages)
Does this study help to answer the key question (compare with PICO items)?
☐ yes ☐ partial ☐ no → consider stopping this assessment
Does the study address an appropriate and clearly focused question?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is the study's methodology rigorous (e.g. exclusion and inclusion criteria and methodology for data extraction)?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is the literature search rigorously enough (e.g. Medline, Embase and Cochrane combined with hand searching of key journals/reference lists) to identify all relevant studies?
☐ yes ☐ partial ☐ no/unknown/not applicable
Has the individual study's quality been assessed and taken into account?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is there enough similarity (e.g. use of heterogeneity test) between the individual studies selected to make combining them reasonable?
☐ yes ☐ partial ☐ no/unknown/not applicable
Overall assessment (based on previous questions**)**
Did the study minimize bias (this is the case if almost all criteria have been fulfilled or if not the conclusions are thought very unlikely to alter)?
☐ yes ☐ partial

☐ no
What is the consequence of this quality assessment?
☐ this study is included and the quality assessment has no consequences for its grading (high quality) ☐ this study is included, but the quality assessment can have negative consequences for its grading (moderate quality) ☐ this study is rejected (low quality)

G2 Quality assessment checklist: randomized controlled trials

Based on SIGN methodology checklist 2: randomised controlled trials[8] and the methodological quality assessment's checklist by Downs and Black[33].

Name assessor
Bibliography (author, journal, year, volume and pages)
Does the study address an appropriate and clearly focused question?
☐ yes ☐ partial ☐ no/unknown/not applicable
Does this study help to answer the key question (compare with PICO items)?
☐ yes ☐ partial ☐ no → consider stopping this assessment
Are participants assigned to treatment groups by random allocation (randomization)?
☐ yes ☐ no/unknown/not applicable → consider stopping this assessment
Is an adequate allocation concealment method (e.g. centralized, computerized or third-party assignment) used?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are participants, investigators and care-givers kept unaware (blind) about treatment allocation?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are the participants' characteristics (e.g. inclusion and exclusion criteria) clearly described?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are the interventions of interest clearly described?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are relevant outcomes measured in a standard, valid and reliable way?
☐ yes

☐ partial ☐ no/unknown/not applicable
What is the drop out rate (individuals dropped out/all individuals randomized) of the study?
……..%
Are all participants analyzed within the treatment group to which they were randomly allocated (intention-to-treat analysis)?
☐ yes ☐ no/unknown
Has potential confounding been analyzed and taken into account?
☐ yes ☐ partial ☐ no/unknown/not applicable
Overall assessment (based on previous questions**)**
Did the study minimize bias (this is the case if almost all criteria have been fulfilled or if not the conclusions are thought very unlikely to alter)?
☐ yes ☐ partial ☐ no
What is the consequence of this quality assessment?
☐ this study is included and the quality assessment has no consequences for its grading (high quality) ☐ this study is included, but the quality assessment can have negative consequences for its grading (moderate quality) ☐ this study is rejected (low quality)

G3 Quality assessment checklist: observational/case-control studies

Based on SIGN methodology checklists 3: cohort studies[8], 4: case-control studies[8] and the methodological quality assessment's checklists by Downs and Black[33].

Name assessor
Bibliography (author, journal, year, volume and pages)
Does the study address an appropriate and clearly focused question?
☐ yes ☐ partial ☐ no/unknown/not applicable
Does this study help to answer the key question (compare with PICO items)?
☐ yes ☐ partial ☐ no → consider stopping this assessment
Are the participants' characteristics (e.g. inclusion and exclusion criteria) clearly described?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are the participants' groups studied selected from source populations comparable in all respects other than the factor(s) under investigation?
☐ yes ☐ partial ☐ no/unknown/not applicable
What is/are the participation rate(s) (number of participants/all persons invited) in this study?
……. %
Is the assessment of exposure measured in a valid and reliable way?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are the outcomes defined and measured in a valid and reliable way?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are the assessors of outcome unaware (blind) about exposure status?
☐ yes ☐ partial

☐ no/unknown/not applicable
What is the drop out rate (individuals dropped out/all individuals included) of the study?
……..%
Are those lost to follow-up compared with the full participants by exposure status?
☐ yes ☐ no/unknown
Are main potential confounders been identified and taken into account in the design and analyses?
☐ yes ☐ partial ☐ no/unknown/not applicable
Have confidence intervals been provided?
☐ yes ☐ no
Overall assessment (based on previous questions**)**
Did the study minimize bias (this is the case if almost all criteria have been fulfilled or if not the conclusions are thought very unlikely to alter)?
☐ yes ☐ partial ☐ no
What is the consequence of this quality assessment?
☐ this study is included and the quality assessment has no consequences for its grading (high quality) ☐ this study is included, but the quality assessment can have negative consequences for its grading (moderate quality) ☐ this study is rejected (low quality)

G4 Quality assessment checklist: diagnostic accuracy studies

Based on SIGN methodology checklists 5: studies of diagnostic accuracy[8] and the methodological quality assessment's checklists by Irwig et al.[34].

Name assessor
Bibliography (author, journal, year, volume and pages)
Does the study address an appropriate and clearly focused question?
☐ yes ☐ partial ☐ no/unknown/not applicable
Does this study help to answer the key question (compare with PICO items)?
☐ yes ☐ partial ☐ no → consider stopping this assessment
Are the participants' characteristics (e.g. inclusion and exclusion criteria) clearly described?
☐ yes ☐ partial ☐ no/unknown/not applicable
Are the participants representative of the patients who will receive the test in daily practice (according to the described inclusion and exclusion criteria)?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is the index test (test to be investigated) described clearly to permit test replication?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is the reference standard likely to classify the condition correctly (high specificity and sensitivity)?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is the period between reference standard and index test valid (no expected change in target condition)?
☐ yes ☐ partial ☐ no/unknown/not applicable
Is the index test no part of the reference standard?

☐ yes ☐ no/unknown
Is the reference standard used for all participants?
☐ yes ☐ no/unknown/not applicable
Is the same reference standard used in all participants?
☐ yes ☐ no/unknown/not applicable
Are the index test and reference standard measured independently (blind to each other)?
☐ yes ☐ no/unknown/not applicable
Are the index test and reference standard measured independently of other clinical information?
☐ yes ☐ no/unknown/not applicable
Are uninterpretable or intermediate test results reported?
☐ yes ☐ no/unknown/not applicable
What is the withdrawal rate (individuals withdrawing/all individuals included) from the study?
……. %
Overall assessment (based on previous questions**)**
Did the study minimize bias (this is the case if almost all criteria have been fulfilled or if not the conclusions are thought very unlikely to alter)?
☐ yes ☐ partial ☐ no
What is the consequence of this quality assessment?
☐ this study is included and the quality assessment has no consequences for its grading (high quality) ☐ this study is included, but the quality assessment can have negative consequences for its grading (moderate quality) ☐ this study is rejected (low quality)

Appendix H

Template evidence table for intervention studies

Bibliography	Study type	Evidence level	No. patients	Patients characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Funding	Comments
example											
Shaker, et al. Fertil Steril 1996;65:992-6	RCT		26	IVF patients at risk for OHSS defined as E2 > 3,540 pg/ml age 34 years duration subfertility (4.4 years)	albumin infusion on day ovum pick-up and 5 days later + fresh embryo transfer	cryo-preservation all embryos		severe/ moderate OHSS clinical pregnancy/woman	OR (95% CI) 5.3 (0.5-56.2) 0.06 (0.01-1.2)		

Bibliography	author, journal, year, volume and pages
Study type	meta-analysis, systematic review, randomized controlled trial, non-randomized study, case report, opinion documents etc.
Evidence level	see appendix J
No. patients	total number of patients included in the study: e.g. cases vs. controls, started vs. completed
Patient characteristics	relevant patient/setting characteristics: e.g. country, age, disease status, definition disease status, secondary or tertiary care inclusion criteria
Intervention	characteristics treatment/procedure studies as intervention: e.g. length of treatment
Comparison	treatment/procedure compared with the studied intervention: e.g. placebo or alternative treatment
Length of follow-up	duration patients participate the study from inclusion to a specified end-point (e.g. implantation) or the end of data collection
Outcome measures	all outcome measures (positive and negative): e.g. OHSS occurrence rate, implantation rate, quality of life, satisfaction
Effect size	for instance absolute risk reduction, relative risks, numbers needed to treat/harm, or odds ratios with confidence intervals
Funding	source of funding/grants e.g. governmental, voluntary/charity or pharmaceutical industry
Comments	additional characteristics/interpretations or flaws of the study

Appendix I

Template evidence table for diagnostic studies

Bibliography	Study type	Evidence level	No. patients	Prevalence	Patients characteristics	Type of test	Reference standard	Sensitivity	Specificity	Predictive value (+)	Predictive value (-)	Funding	Comments
example													
Lee, et al. Hum Reprod 2008;23:160-7	cohort study		262	8%	one cycle controlled ovarian stimulation exclusion: ultra-long/short or antagonist protocols, oocyte donation	basal serum AMH	moderate or severe OHSS according to Navot	91%	81%	30%	99%		

Bibliography	author, journal, year, volume and pages
Study type	meta-analysis, systematic review, randomized controlled trial, non-randomized study, case report, opinion documents etc.
Evidence level	see appendix J
No. patients	total number of patients included in the study
Prevalence	proportion patients with the disease in the total population at risk
Patient characteristics	relevant patient/setting characteristics: e.g. country, age, disease status, definition disease status, secondary or tertiary care
Type of test	characteristics of the test used in the study: e.g. name, threshold levels, methodology
Reference standard	test used as a 'gold' standard and compared with the study test
Sensitivity	proportion individuals classified as positive by the reference standard, who has a positive result by the study test as well
Specificity	proportion individuals classified as negative by the reference standard, who has a negative result by the study test as well
Predictive value (+)	proportion individuals with a positive study test result, who has a positive result by the reference standard as well
Predictive value (-)	proportion of individuals with a negative study test result, who has a negative result by the reference standard as well
Funding	source of funding/grants e.g. governmental, voluntary/charity or pharmaceutical industry
Comments	additional characteristics/interpretations or flaws of the study

Appendix J

Template for level of evidence/recommendation class/phrasing

studies	**level of evidence**	**Study Quality**	**recommendation class**	**recommendation phrasing**
meta-analysis multiple randomized trials	A	high	I	should is recommended/indicated is useful/effective/beneficial
		high	III	should not is not recommended/indicated is not useful/effective/beneficial may be harmful
		moderate	IIa	is reasonable can be useful/effective/beneficial is probably recommended/indicated
single randomized trial large non-randomized trial(s)	B	high		
		moderate	IIb	may/might be considered/reasonable the usefulness/effectiveness is unknown/unclear/uncertain the usefulness/effectiveness is not well established
retrospective studies case studies experts' opinions	C	high-moderate		
no studies	no evidence		GPP	the GDG recommends

Appendix K

Template comments processing report

The following template will require ESHRE guideline developers to provide a short report of the consultation process and how comments were handled.

Date	Biography	Represents	Page & Line numbers	Comments	Consequence	Date response
example						
March 21, 2011	Dr. A. Bbbbb (Belgium)	SIG Andrology	p. 6 lines 131-5	asking for something outside the guideline's scope	subject is out of the guideline's scope and therefore not covered	March 25, 2011
March 23, 2011	Dr. C. Dddd (USA)	ASRM	p.2 line 38	typing error	correction has been made	March 25, 2011

Date	date of comment's receipt
Biography	name reviewer, country
Represents	representative of e.g. Advisory Committee/SIG/associated organizations
Page & Line numbers	page and line numbers of the original document to find the comment's concerning part
Comment	comment on the guideline's draft version
Consequence	consequences of the comment proportion patients with the disease in the total population at risk
Date response	date that the reviewer is informed about the consequences of its comments