

1. Initiation of guideline production or revision

The proposal to produce a new guideline, or to revise an existing guideline, can be made by any member of the European Branch of the IUSTI (IUSTI-Europe), or by members of the other partner organisations (see: <https://iusti.org/treatment-guidelines/>).

The decision to produce a new European guideline, or to revise and update an existing one, will be made by the Editor-in-Chief advised by the board.

2. Selection of authors and editors

An editor will be appointed to oversee the production of each guideline. The Editor, usually a member of the IUSTI-Europe editorial board, will be appointed by the Editor-in-Chief. A lead author for the guideline will be identified and co-authors will be invited to produce the guideline on behalf of IUSTI and partner organisations by the appointed Editor. The editor, lead author and co-authors form the guideline development group (GDG).

A guideline must be co-authored by at least two people, from different European countries [1].

Suggestions for authors can be obtained by contacting –

- Members of the Editorial Board (including representatives of partner organisations) who will also seek nominations through their own networks of contacts in Europe.
- Members of the IUSTI Europe Council (by emailing the Secretary).

As the involvement of a large number of authors tends to lead to a delay, the number of authors should be limited. It is expected that there will usually be between three and six authors, from several different European countries. Editors must ensure the authors represent appropriate diversity as relevant to the guideline topic. Potential conflicts of interest should be checked by collecting declarations of conflict of interest from the authors (and the lead editor). Where possible, representation should be sought from a relevant patient support group within Europe.

The guideline editor will place a brief announcement via the IUSTI-Europe Secretary, on the IUSTI website (<https://iusti.org/treatment-guidelines/>) containing the following information: the guideline is being produced / updated; the names of the authors; the name and e-mail address of the guideline editor and an invitation for interested parties to contact them if they wish to contribute to the process.

3. Revision/update of existing guideline

All guidelines are reviewed on a regular basis. If it is decided that an update is required then the editor and lead author should agree the extent of the update required.

An update search is carried out looking for evidence based guidelines, and systematic reviews published since publication of the last version of a guideline. These searches are based on the key questions and search strategies used in the original guideline.

If only minor amendments are made, these will be published on the website with the updated content appearing in red for 6 months from the date of the update. To ensure that appropriate indexing takes place a letter should be sent to the editor of the journal where the guideline was originally published.

For more major revisions, follow the process below

4. Formulation of clinically important questions

The GDG should first produce a list of the most important questions for which the guideline should provide answers. This will ensure that the guideline has a clear aim and focus, and it will guide the next stage of the production process which is obtaining all the relevant evidence by means of a literature review.

One generally accepted approach of formulating these research questions is by using the **PICO** method (**P**opulation, **I**ntervention, **C**omparator, **O**utcome).² Note that the intervention could be a diagnostic test or a drug treatment, and the outcome could be an infection (or complication), the sensitivity and specificity of a test, or efficacy in curing an infection.

Ideally, the population will be adult patients attending a dermato-venereology (or sexual health) clinic in the WHO Europe region. Evidence from non-European settings can be considered when appropriate with considerations to be given to the implementation of guidelines recommendations. The GDG should focus on the most important questions that the guideline needs to answer – as a guide between four and eight questions will usually be sufficient. The PICO approach is most useful when comparing one treatment intervention to another treatment (or to no treatment). It is not always applicable in other situations and it should be remembered that the essential step is to produce a list of the most clinically important questions which can be done without using a strict PICO approach.

Examples of PICO questions:

- *“Who should be tested for hepatitis B virus (HBV) infection in order to identify HBV infections or persons with no evidence of past infections that are eligible for vaccination?”*

Population: adult patients with risk factors (e.g. men who have sex with men, commercial sex workers) and in patients without those risk factors attending a dermato-venereology (or sexual health) clinic in the WHO Europe region.

Intervention: serology testing for markers of HBV infection or immunity in patients with risk factors

Comparator: no serology testing.

Outcome: identification of persons infected with HBV and persons at risk of HBV infection who could benefit from HBV vaccination.

- *“What is the effectiveness ceftriaxone vs ciprofloxacin in obtaining microbiological cure of gonorrhoea infection in adult patients?”*

Population: adult patients who are diagnosed with gonorrhoea.

Intervention: specific antibiotic(s) e.g. ceftriaxone

Comparator: a different antibiotic e.g. ciprofloxacin.

Outcome: microbiological cure of gonorrhoea.

The choice of the outcomes to be considered should include patient-relevant outcomes. The relative importance of the outcomes for making recommendations should be evaluated at the beginning of the guideline development. The PICO questions will be shared with the editorial board at an early stage of the guideline development.

More detailed information on formulating the guideline key questions and rating the importance of outcomes can be found in Guyatt et al [2]

5. Review of the literature

A thorough and systematic literature review must be undertaken to obtain the evidence base for the production of the guideline.[3] This includes the documentation and transparent reporting of each step of the systematic literature assessment such as specified in the PRISMA 2020 checklist (<https://www.prisma-statement.org/PRISMAStatement/Checklist>). The authors may consider the registration of the literature review protocol in PROSPERO database (<https://www.crd.york.ac.uk/prospero/>) where they can also look up for previously undertaken reviews of interest.

Essential steps include:

- Searching for and evaluating aggregate evidence (existing guidelines and published systematic reviews and meta-analyses or reviews of reviews):
 - Desk review of relevant European country national association guidelines, eg, UK national guidelines (produced the British Association for Sexual Health and HIV [BASHH]), or guidelines issued by the German STI association (DSTIG), etc.
 - Review of relevant guidelines produced by the US Centres for Disease Control
 - Review of relevant guidelines produced by the World Health Organisation
 - Search The Cochrane Database of Systematic Reviews
 - Search Medline and Embase for systematic reviews and meta-analyses
- Performing systematic literature searches for primary studies, if this is necessary to answer the PICO questions (eg, because no or inadequate aggregate evidence was identified or because it needs to be updated):
 - Search The Cochrane Central Register of Controlled Trials (CENTRAL)
 - Search Medline and Embase
 - Depending on the guideline, other sources of literature may need to be reviewed

The search strategies and the PRISMA flowchart should be kept for documentation and review.

6. Certainty of the evidence and strength of recommendations

The literature assessment includes an evaluation of the certainty of the evidence – this forms the basis to formulate recommendations using a standard wording [4]. Many different approaches to classifying the quality of the evidence and strength of recommendation exist and can be used or adopted for developing guidelines. We favour adoption of the GRADE approach.

The GRADE system looks at the **strength** of the recommendation and the **certainty** (or quality) of the evidence to support it. The GRADE Handbook explains:

“...the quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation. Guideline panels must make judgments about the quality of evidence relative to the specific context for which they are using the evidence. The strength of a recommendation reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended”. [5]

The **certainty of evidence** is rated on an outcome level for each comparison of interventions. GRADE defines four distinct levels of certainty, from high to very low and defines these as follows:

High certainty (++++) means that the review authors have a lot of confidence that the true effect lies close to the estimate of the effect derived from the literature.

Moderate certainty (+++O) means that the review authors believe that the true effect is probably close to the effect estimated from the literature.

Low certainty (++OO) means that the true effect might be markedly different from the effect estimate derived from the literature review.

Very low certainty (+OOO) means that the true effect is probably markedly different from the effect estimate derived from the literature review.

To determine the certainty of the evidence for each outcome, various domains are considered to rate down certainty (1. Risk of Bias, 2. Imprecision, 3. Inconsistency, 4. Indirectness, 5. Publication Bias) or to rate up certainty of the evidence (1. Large magnitude of effect, 2. Dose-response gradient, 3. Residual confounding would decrease magnitude of effect). If the effect estimate is derived from randomised trials, it starts with a high certainty and domains to rate up certainty of the evidence are usually not considered. If the effect estimate is derived from observational studies, it starts with a low certainty and both the domains to rate down and rate up certainty are considered. Detailed guidance on the process of rating the certainty of the evidence is given in the GRADE guidelines series published in the Journal of Clinical Epidemiology [6-13].

The **strength** of the recommendation is graded as 1 (strong recommendation) or 2 (weak recommendation), and should be expressed using a standardised wording and symbols throughout the guideline document.

A **Grade 1** recommendation is a **strong recommendation** to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording: 'We recommend ...' or 'It is recommended ...'

A **Grade 2** recommendation is a **weaker or conditional recommendation**, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording: 'We suggest ...' or 'It is suggested ...'. The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences, and, where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

Detailed information on how to formulate recommendations and determine the strength of recommendations can be found in the GRADE guidelines series published in the Journal of Clinical Epidemiology [14,15].

An optional step is the organisation of a workshop of invited experts to discuss and decide upon controversial issues pertaining to the diagnosis and management of a condition. The experts can be asked to prepare discussion (scientific background) papers in advance, using the format of key questions, review of data and proposed answers, as previously used in IUSTI/WHO Europe workshops for invited experts. These papers, with the comments given during the workshop, can be used to assist in the subsequent writing/updating of the guideline and can be used to inform all those interested in the field. The responsibility for organising such a workshop in the name of IUSTI Europe should be clearly delegated to a suitable individual by the Editor-in-Chief.

7. Format

As the main purpose of the guideline is to help a clinician decide what to do in a given clinical situation, it is essential that the guideline is concise and readable. An indicative word count would be 1,500 to 3,000 words, excluding tables. A guideline is **not a review article**, so should not include substantial blocks of text explaining the details of studies underpinning the recommendations. However, in order to be transparent about the development and reasoning for the recommendations, a guideline needs to include brief information on the link between evidence and recommendations. Detailed information about the evidence can be included in appendices or as a separately published review article.

Recommendations must be clear, unequivocal and actionable. Where there is more than one acceptable option, then it should be made clear whether there is a clear order of preference, i.e. first-line, second-line etc., or where the evidence does not allow a definite distinction to be made between the options (that is, they are regarded as equivalent).

Recommendations must address the key elements required for the management of a case, including diagnosis, treatment, partner notification and what information should be given to the patient.

To ensure brevity and clarity, there should be use of sub-headings, and the use of bullet points is strongly encouraged to break up the text in a logical fashion.

It may be helpful to the user/reader of the guideline to put key recommendations in a separate box, and to include an algorithm/flow-chart.

A typical set of sub-headings to be used would be as follows:

Title – e.g. “2023 European guideline on ...”

- Authors
- Lead editor (if published in a journal the lead editor’s name should be included in the list of authors, in a position to be decided by the lead author).
- A brief introduction which may cover aetiology and transmission, symptoms, signs and complications in a single paragraph
- The clinically important questions with recommendations under the following headings
 - Diagnosis
 - Management
 - Therapy
 - Partner notification
 - Follow up
 - Prevention/health promotion
- Proposed review date
- Acknowledgements
 - List (by alphabetic order of surname) persons, other than the authors, who have made a contribution to the guideline.
- Composition of editorial board (refer to document at: <https://iusti.org/wp-content/uploads/2022/03/Editorial-Board-2022.pdf>)
- References: A full list of referenced source materials must be provided at the end of the guideline. All significant statements made in the guideline should be referenced with respect to these sources in the usual way.
- Appendices:
 - Search strategy in electronic databases

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- PRISMA checklist
- Tables of levels of evidence and grading of recommendations xxx
- Statement on declarations of interest (see appendix)

8. Declarations of interests

Each author and editor involved in the production of a guideline will be asked to make a written declaration of interests utilising a standard form. A summary of this will form part of the guideline and be published with it. Authors will return their declarations to the editor of their guideline; editors will return their declarations to the Editor-in-Chief who may ask for an author to be recused if there is a significant concern.

9. Review

Each guideline should contain a suggested date for future review usually within 5 years.

10. Consultation

To ensure that the final guideline represents and considers the variations in national health systems characteristics and epidemiological context of the IUSTI-Europe member countries as well as the views of the relevant stakeholders, the draft guideline will undergo an external review procedure as part of the guideline development.

Once the final draft guideline has been produced by the authors, it will be sent to the editor who will undertake the formal 3-month review process including the following steps -

- To be placed on the IUSTI website
- To be sent to all members of the European STI Guidelines Editorial Board for comments and, in the case of the liaison representatives of partner organisations, to be circulated as required by the relevant organisation.
- To be circulated via Secretary of IUSTI Europe to members of the IUSTI Europe Council asking them to read the guideline themselves, and also to send the guideline to one or more experts in their respective countries. All comments to be sent to both the lead author and the editor with 3-month deadline.
- The authors to suggest to the editor one or more experts in the field who could be approached to give an independent opinion on the guideline (this step may be omitted if the guideline is to be submitted to a journal whose editor is going to send it out for peer-review).

11. Finalising the guideline

Any comments obtained through the consultation exercise to be discussed between the editor and the co-authors, and agreement reached by a process of consensus to produce the final version of the guideline.

The final version of the guideline can only be signed off as an accepted formal European STI Guideline by the Editor-in-Chief.

12. Publication and dissemination

This is the responsibility of the lead editor and the lead author. The guideline may be published solely in electronic form on the IUSTI website, or paper publication in a journal may simultaneously be sought (it is particularly appropriate to publish in the *International Journal of STD & AIDS* as this is the official organ of the IUSTI, but the *Journal of the European Academy of Dermatology and Venereology* should also be considered). If published in a journal then the lead editor's name should be included in the list of authors, in a position to be decided by the lead author. Scientific back-ground papers, if produced, may be published solely in electronic form or submitted for paper publication in a journal.

13. References:

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6. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology*. 2011;64(4):383-94.
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12. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of clinical epidemiology*. 2011;64(12):1303-10.
13. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *Journal of clinical epidemiology*. 2011;64(12):1311-6.
14. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013 Jul;66(7):719-25. doi: 10.1016/j.jclinepi.2012.03.013.
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